効果[28)29)]との関連性だけでなく，感染経路の検討に有用であるが，本邦のHCVキャリアでのgenotypeは主として1b型が80%を占めており，次いで2a型，2b型である[28)-30)]。

3. 治　　療

C型急性肝炎は高率に慢性化するため，1～3ヵ月の観察で，血中よりHCVRNAが消失していない場合，積極的にIFN療法を行うことが望ましいと思われる。急性肝炎に対するIFN療法の効果は80%と慢性肝炎の30%に比較して高率で，完全に慢性肝炎となってからIFNを投与するより有効であると考えられる。その際，感染初期であれば4週間の短期投与でも効果があることが証明されている[31)]。C型急性肝炎に対するIFN療法は医療現場での針刺し事故などによる感染の場合，労働災害として保険適応であるが，他の感染経路による場合は保険適応でははない。

慢性肝炎には1992年から一般にIFN療法が行われるようになったが，IFNは肝機能の改善だけでなく，ウイルスの排除[28)29)]，さらには肝臓癌発症の防止効果が疫学的[32)]にも，実験的[33)]にも認められている。IFN単独療法では，ウイルスが持続的に陰性化する著効例は約30%である。著者らは311例のC型慢性肝炎あるいは肝硬変に天然型IFNαを投与し，HCVRNAが持続的に陰性化する予測因子について多変量回帰分析を用いて検討した[28)29)]。その結果，高HCVRNA量およびgenotype 1b型の著効率は5%しかないことが判明した。現在，このような例は難治性C型慢性肝炎と呼ばれている。これらの症例へのIFN療法が重要となり，現在，週1回投与のpegIFNα-2bとリバビリ併用療法が行われている。著者らが九州大学関連肝疾患研究会として行っている成績では，このような難治性C型慢性肝炎での著効率は約40%と以前のIFN単独療法に比較し著明に増加した。しかし，著者らが以前より指摘していたが，女性および高齢者の著効率が低いことが課題に残されている[29)34)]。

4. 予　　防

B型肝炎の予防の項で述べたように，HCVキャリアへ日常の自己管理と他人への感染予防についてはB型肝炎の場合と同様のこと（B型肝炎の項を参照）を指導する必要がある。

性行為によるHCV感染は，セックスパートナーの一方がHCVキャリアである場合に起こる。ワクチンも開発されておらず，コンドームの使用以外，予防方法はないが，幸いに夫婦間感染率も少なく，特別な措置は必要ないと思われる。しかし，特殊浴場女性従業員でのHCV感染率が高いことから，夫婦間以外での性行為による感染の危険は高く，米国のCDCが指導しているように，セックスパートナーを減少させることも，一つの予防対策と考えられる。

お　わ　り　に

肝炎ウイルスを性感染症の観点から述べた。性感染症としてHAV，HBVおよびHCVが重要と考えられる。その他HGV，TTVについては未だ明確でなく，HEVについては現在まったく不明で，今後の検討が待たれる。

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HEPATOLOGY

Association between the treatment length and cumulative dose of pegylated interferon alpha-2b plus ribavirin and their effectiveness as a combination treatment for Japanese chronic hepatitis C patients: Project of the Kyushu University Liver Disease Study Group

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Abstract

Aim: The aim of the present study was to investigate the association between the length of the treatment period and the cumulative dose of pegylated interferon alpha-2b (peg-IFN alpha-2b) plus ribavirin (RBV) and their effectiveness in the treatment of chronic hepatitis C.

Methods: Seven hundred and fifteen patients received peg-IFN alpha-2b plus RBV treatment for 48 weeks and 24 weeks for genotypes 1 ($n = 586$) and 2 ($n = 129$), respectively.

Results: Sustained virological responses (SVR), defined as serum hepatitis C virus (HCV)-RNA undetectable at 24 weeks after the end of treatment, were 42.4% and 74.4% in genotypes 1 and 2, respectively, on an intention-to-treat analysis. SVR significantly increased with treatment length (4.7%, 36.4%, and 51.8% for < 24 weeks, 24–47 weeks, and 48 weeks, respectively, for genotype 1; and 28.6%, 57.1%, 78.3% for < 12 weeks, 12–23 weeks, and 24 weeks, respectively, for genotype 2). SVR significantly increased with total cumulative treatment dose (21.1%, 36.5%, and 52.9% with < 60%, 60–79%, and ≥ 80% in peg-IFN dose; 29.6%, 51.1%, and 59.2% with < 60%, 60–79%, and ≥ 80% in RBV dose) in genotype 1, although it did not differ significantly for genotype 2.

Conclusions: In peg-IFN alpha-2b plus RBV treatment for chronic hepatitis C, it is important to complete the target length of treatment and to continue the target dosage to achieve SVR, especially for genotype 1 patients.

Introduction

Hepatitis C virus (HCV) is a major cause of chronic liver disease, with perhaps 200 million persons infected worldwide. Approximately 1.8 million patients have chronic HCV infection in Japan. The severity of disease varies widely, from asymptomatic chronic infection to cirrhosis and hepatocellular carcinoma (HCC).[1,2] Eradication of HCV by antiviral treatment improves liver histology and patient survival.[3] A currently popular antiviral treatment regimen for the treatment of chronic HCV infection worldwide is pegylated interferon alpha (peg-IFN alpha) in combination with ribavirin (RBV). The combination treatment has resulted in a higher rate of sustained virological response (SVR), over 50% in Caucasian patients, than standard interferon (IFN) monotherapy.[4,5] However, there are no data concerning the response and safety of the combination treatment for a large number of Japanese patients with chronic HCV infection because this treatment was only approved by the Japanese Ministry of Health, Labor and Welfare in December 2004.

The HCV genotype has been reported to be the most important predictor of IFN treatment response.[4–14] Patients infected with genotypes 2 and 3 achieved approximately 65% SVR in a 24-week

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trial of non-peg-IFN alpha in combination with RBV, in contrast to patients with genotype 1 who had < 30% SVR.[13,14] SVR is also achieved consistently more often by patients with a low HCV-RNA level.[4–14] Moreover, host factors affect the chance of SVR, albeit less so than the genotype.[10] These factors include age, race, sex, obesity, and the degree of hepatic fibrosis and steatosis.[15] In a racial analysis, African Americans were shown to have response rates only one-half to one-third those of Caucasians.[15] In addition, Asian patients were more likely to achieve an SVR by treatment with peg-IFN alpha-2a and RBV than Caucasian patients.[16] The reasons for the racial differences in response rates to peg-IFN alpha plus RBV treatment are not well known.

Peg-IFN alpha was a substantive breakthrough in therapy because of the longer effect; the lasting, steady therapeutic blood level is a major pharmacokinetic advance.[4,5] The most frequent adverse effects during peg-IFN alpha plus RBV treatment are depression and hematological disorders such leukopenia, anemia, and thrombocytopenia. Therefore, the peg-IFN alpha plus RBV treatment often results in discontinuation or the need for a reduction of the dosage due to the adverse effects.

To investigate the efficacy and safety of antiviral treatments for Japanese chronic hepatitis B and C patients, a multicenter study, the Kyushu University Liver Disease Study (KULDS), was launched in 2003. Our group has previously reported several clinical studies.[17–21] The present report is a prospective, multicenter study carried out to analyze the association between the treatment length and the cumulative dose and effectiveness of peg-IFN alpha-2b plus RBV treatment for a large number of Japanese patients with chronic hepatitis C.

Methods

Patients

Treatment of chronic hepatitis C with a combination of peg-IFN alpha-2b and RBV was accepted by the Japanese Ministry of Health in October, 2004. A prospective study of 715 Japanese patients aged 18 years or older (586 and 129 patients with genotypes 1b and 2, respectively) treated with peg-IFN alpha-2b plus RBV between December 2004 and February 2007 who were all positive for antibody to HCV and HCV-RNA for over 6 months was carried out. The respective distribution rates were 82.0% and 18.0% for genotypes 1b and 2, similar to the reported epidemiological distribution.[22]

Criteria for exclusion were: (i) clinical or biochemical evidence of hepatic decompensation, advanced cirrhosis identified by large esophageal varices (F2 or F3), history of gastrointestinal bleeding, ascites, encephalopathy, or hepatocellular carcinoma; (ii) hemoglobin level < 115 g/L, white blood cell count $< 3 \times 10^9$/L, and platelet count $< 50 \times 10^9$/L; (iii) concomitant liver disease other than hepatitis C (hepatitis B surface antigen positive or HIV positive); (iv) excessive active alcohol consumption > 60 g/day or drug abuse; (v) severe psychiatric disease; and (vi) antiviral or corticosteroid therapy within 12 months prior to the enrollment. Patients who fulfilled the above criteria were recruited at Kyushu University Hospital and 32 affiliated hospitals in the northern Kyushu area of Japan.

Within the 3 months before the start of the treatment and every 3 months during the treatment period, each patient was tested for alpha-fetoprotein (AFP) and had abdominal ultrasonographic examination. If an abnormal AFP level of ≥ 40 ng/mL and/or an appearance of focal lesions at ultrasonographic examination was found at any testing, further testing for hepatocellular carcinoma (HCC) was done, which included dynamic computed tomography (CT), angiography, and/or tumor biopsy. Patients so confirmed to have HCC within 3 months after the start of the treatment were excluded from this study.

Table 1 shows the baseline characteristics of the enrolled patients. The median age was 58.0 years. Of the 715 patients, 198 (27.6%) were aged 65 years or over. In Japan, many older patients with chronic hepatitis C are candidates for antiviral treatment, different from many other countries. The rates of prior non-peg-IFN monotherapy significantly differed among the genotype-classified patients (genotype 1, 40.8% and genotype 2, 28.7%).

Table 1 Characteristics of 715 chronic hepatitis C patients treated with a combination of pegylated IFN alpha-2b and ribavirin, classified by HCV genotype

Characteristics	Total $n = 715$	Genotype 1 $n = 586$	Genotype 2 $n = 129$	*P*-value
Male *n* (%)	388 (54.3)	321 (54.8)	67 (51.9)	0.6250
Age (years)	56.8 ± 11.7	57.8 ± 10.3	52.6 ± 14.1	0.0004
Body mass index (kg/m^2)	23.4 ± 3.2	23.5 ± 3.1	23.5 ± 3.3	0.4999
Prior IFN monotherapy *n* (%)	276 (38.6)	239 (40.8)	37 (28.7)	0.0140
Prior combined IFN plus RBV treatment *n* (%)	69 (9.7)	60 (10.9)	5 (3.9)	0.0221
Alanine aminotransferase (IU/L)	77.1 ± 55.4	77.5 ± 52.8	70.9 ± 55.3	0.0594
γ-Glutamyltranspeptidase (IU/L)	60.6 ± 60.3	61.8 ± 58.6	50.8 ± 45.2	0.0241
Albumin (g/dL)	4.1 ± 0.4	4.1 ± 0.3	4.1 ± 0.3	0.1305
White blood cell (/mm^3)	5030.8 ± 1439.2	4993.0 ± 140.8	5260.6 ± 1658.2	0.3005
Hemoglobin (g/dL)	13.9 ± 1.4	13.9 ± 1.4	13.9 ± 1.5	0.7092
Platelet count (10^9/L)	165 ± 56	161 ± 52	185 ± 69	0.0013
Creatinine (mg/dL)	0.70 ± 0.16	0.70 ± 0.17	0.71 ± 0.16	0.1230
Creatinine clearance (mL/min)	97.9 ± 29.9	97.1 ± 29.8	101.3 ± 31.3	0.3621

Data are shown as the mean ± standard deviation.
HCV, hepatitis C virus; IFN, interferon; RBV, rivabirin.

Also, the rates of prior non-peg-IFN alpha plus RBV treatment significantly differed (genotype 1, 10.9% and genotype 2, 3.9%). These differences are explained by the necessity of re-treatment of patients with genotype 1 who had lower SVR by the standard IFN monotherapy than did non-genotype 1 patients, and because the RBV combination treatment with peg-IFN alpha-2b was approved in stages, first for patients with genotype 1 in October 2004, then for those with non-genotype 1 in January 2006. The means for age, platelet count, and γ-glutamyltranspeptidase (γ-GTP) in genotype 1 patients were significantly different than those of genotype 2 patients.

Informed consent was obtained from all patients before enrollment in this study. The study was approved by the institutional ethics committees of the hospitals involved and conducted in accordance with the ethical guidelines of the Declaration of Helsinki and the International Conference on Harmonization of guidelines for good clinical practice.

Treatment regimen

All patients were treated with a weight-based, 1.5 μg/kg weekly dose of subcutaneous peg-IFN alpha-2b (PegIntron A; Schering-Plough, Osaka, Japan). In combination with peg-IFN alpha-2b, RBV (Rebetol; Schering-Plough) was given orally at a daily dose of 600–1000 mg based on bodyweight (600 mg for patients weighing < 60 kg, 800 mg for those weighing 60–80 kg, and 1000 mg for those weighing ≥ 80 kg). The lengths of treatment were 48 weeks and 24 weeks for HCV genotypes 1 and 2 patients, respectively. The above durations and dosages are those approved by the Japanese Ministry of Health, Labor and Welfare. Patients were considered to have RBV-induced anemia if the hemoglobin level decreased to < 100 g/L. In such cases, a reduction in the dose of RBV was required. Some patients also had peg-IFN alpha-2b-induced psychological adverse effects or a decrease of white blood cell and platelet count. In such cases, a reduction in the dosage of peg-IFN alpha-2b was required. Both peg-IFN alpha-2b and RBV were discontinued if the hemoglobin level, white blood cell count, or platelet count fell below 85 g/L, 1×10^9/L, and 2.5×10^9/L, respectively. The treatment was discontinued if severe general fatigue, hyperthyroidism, interstitial pneumonia, or severe hemolytic problems developed, continuation of treatment was judged not to be possible by the attending physician, or the patient desired discontinuation of treatment.

Clinical and laboratory assessment

Body mass index (BMI) was calculated as weight in kilograms/height in square meters. Blood samples were taken on enrollment, in the morning after 12 h overnight fasting. Serum levels of alanine aminotransferase (ALT), γ-GTP, white blood cell count, hemoglobin, and platelet count were measured by standard laboratory techniques at a commercial laboratory.

Determination of baseline HCV-RNA level and HCV genotype

The pretreatment, baseline, serum HCV-RNA level was measured by a quantitative HCV-RNA polymerase chain reaction (PCR) assay (COBAS Amplicor HCV Monitor Test v2.0 using the 10-fold dilution method; Roche Diagnostics, Tokyo, Japan), which has a lower limit of quantitation of 5000 IU (1350 copies)/mL (5 kIU/mL) and an outer limit of quantitation of 5 100 000 IU/mL (5100 kIU/mL). The HCV genotype was determined by a type-specific primer from the core region of the HCV genome. The protocol for genotyping was carried out as previously described.[23]

Efficacy of treatment

Sustained virological response was defined as serum HCV-RNA undetectable at 24 weeks after the end of treatment. Patients who had undetectable HCV-RNA within the initial 12 weeks of treatment were considered to have had an early virological response (EVR). These efficacy variables, SVR and EVR, were defined as non-detectable HCV-RNA as measured by the COBAS Amplicor HCV Monitor Test v2.0, and the results were labeled as positive or negative. The lower limit of detection was 50 IU/mL (0.5 kIU/mL). The analysis of SVR and EVR was done on an intention-to-treat basis.

Statistical analysis

Continuous data were expressed as mean values, the values ± standard deviation (SD), or the values ± standard error (SE) of the mean. The following statistics were done using a commercially available software package (BMDP Statistical Software Inc., Los Angeles, CA, USA) for the IBM 3090 system computer. The chi-squared or Fisher's exact test was used to examine the association between baseline characteristics and SVR. The Mann–Whitney *U*-test was also used to compare responders and non-responders with regard to various characteristics, when appropriate. The Cochran-Mantel-Haenszel test was used to test for statistical significance among the subgroups. A *P*-value of less than 0.05 was considered significant.

Results

Discontinuation of peg-IFN alpha-2b plus RBV treatment and adverse effects

Of the 715 patients, 152 (21.2%) did not complete peg-IFN alpha-2b plus RBV treatment due to adverse effects or for other reasons (Table 2). Although anemia, as a cause of discontinuation, was followed by general fatigue and depression, most patients discontinued the treatment because of general fatigue and depression together with anemia (hemoglobin 85–100 g/L).

The discontinuation rate was higher for patients with genotype 1 (138 of 586, 23.5%) than those with genotype 2 (14 of 129, 10.8%). The genotype 1 patients included 55 who stopped receiving treatment without virological effect (positive for serum HCV-RNA or no more than 2-$\log_{10}$ reduction from the pretreatment viral level) at 24 or more weeks after the start ($n = 22$), economic problems related to the high cost of treatment ($n = 6$), and other reasons (drop out, moving, nursing ill family members, and being arrested for a crime) ($n = 27$). Thus, the discontinuation rates for patients with adverse effects were only 14.1% (83 of 586) and 7.7% (10 of 129) for genotypes 1 and 2, respectively, with no significant difference. The majority were patients aged 65 years or

Table 2 Reasons for discontinuation of pegylated IFN plus ribavirin treatment, classified by HCV genotype

	Genotype 1	Genotype 2	Total
Adverse effects			
General fatigue	29	0	29
Depression	10	1	11
Encephalopathy	2	0	2
Anemia	11	0	11
Thrombocytopenia	1	1	2
Hyperthyroidism	5	1	6
Rash	6	3	9
Retinopathy	2	0	2
Interstitial pneumonia	1	1	2
Articular rheumatism	1	0	1
Brain infarction	0	1	1
Proteinuria	1	0	1
Hepatocellular carcinoma	11	2	13
Malignancy (extra-liver)[†]	2	0	2
Pulmonary tuberculosis	1	0	1
Other reasons			
No effect of treatment	22	2	24
Economic problems	6	0	6
Others[‡]	27	2	29
Total	138	14	152

[†]Includes one patient with gastric cancer and one patient with lung cancer.

[‡]Includes drop out ($n = 16$), patients who moved ($n = 6$), who nursed ill family members ($n = 3$), or who were arrested for criminal activity ($n = 2$).

over: 68 (73.1%) of the 93 discontinued due to adverse effects. The discontinuation rate due to adverse effects was significantly higher for patients aged 65 years or over (68 of 198, 34.3%) than for those aged under 65 years (25 of 517, 4.8%) ($P < 0.0001$). The mean times to discontinuation (± SD) were 23.0 ± 13.1 weeks and 20.2 ± 15.4 weeks for patients with genotypes 1 and 2, respectively.

SVR by intention-to-treat analysis

Of the 715 patients, 345 (48.2%) achieved SVR in the intention-to-treat analysis. SVR was significantly higher in genotype 2 (96 of 129, 74.4%) than in genotype 1 (249 of 586, 42.4%) ($P < 0.0001$). No significant differences in SVR were found between patients with and without prior non-peg-IFN monotherapy or non-peg-IFN plus RBV treatment between the genotype-classified patients.

An analysis of the association between SVR and the length of treatment showed that patients who completed the combination treatment had a significantly higher rate of SVR than did those with a shortened period of treatment (Fig. 1). Completing the 48-week combination treatment resulted in a significantly higher rate of SVR than either 1–11-week and 12–23-week treatments (both $P < 0.0001$), but there was no significant difference between 24 and 47 weeks and the complete 48 weeks of treatment ($P = 0.1260$). The SVR of patients with genotype 1 was significantly associated with a ≥ 24-week treatment period when compared with treatment < 24 weeks (244 of 481, 50.7% *vs* 5 of 105, 4.7%, $P < 0.0001$). In genotype 2 patients, SVR significantly increased with the treatment period: 28.6%, 57.1%, and 78.3% by 1–11-week, 12–23-week, and 24-week periods, respectively ($P = 0.0018$ by the Cochran-Mantel-Haenszel test).

The combination treatment was done for 443 (75.5%) and 110 (85.2%) of genotype 1 and 2 patients, respectively (Fig. 2). The rates of SVR for genotype 1 and 2 patients were significantly higher in those who continued the combination treatment than in those who discontinued RBV treatment: 230 of 443 (51.9%) versus 19 of 143 (13.2%) genotype 1 ($P < 0.0001$) and 89 of 110 (80.9%) versus seven of 19 (36.8%) genotype 2 ($P = 0.0002$). In genotype 1, 286 patients who required a reduced dosage during treatment (Groups B, C, and D) were able to complete the full 48 weeks of combination treatment. There were no significant differences in SVR among Groups A to D patients with genotypes 1 and 2. Of the patients who discontinued RBV treatment (143 with genotype 1 and 19 with genotype 2), most patients (138 (96.5%) with genotype 1 and 14 (73.7%) with genotype 2) did not complete combination treatment because there was no viral effect, because of adverse effects, or because they dropped out. The remaining patients discontinued the RBV treatment but completed the combination treatment without a reduction of the peg-IFN alpha-2b target dosage (three with genotype 1 and five with genotype 2), or discontinued the RBV treatment and completed their peg-IFN alpha-2b treatment with a reduction of the target dosage (two with genotype 1 and none with genotype 2).

An analysis of the association between SVR and the total dosage of peg-IFN alpha-2b and RBV during the treatment showed that patients with a higher total dosage of the combination treatment had a significantly higher rate of SVR than those with a lower dosage only for genotype 1 patients, although no significant difference was found in genotype 2 (Fig. 3). In genotype 1, reducing the total dosage of peg-IFN alpha-2b during the treatment significantly reduced the rate of SVR: 52.9% (187 of 353) for patients with ≥ 80% of the peg-IFN alpha-2b dosage, 36.5% (30 of 82) for those ≥ 60% but < 80% of the peg-IFN alpha dosage, and 21.1% (32 of 151) for those < 60% of the peg-IFN alpha dosage (both $P < 0.0001$). In genotype 1, the SVR rate of patients < 60% of the RBV dosage (91 of 307, 29.6%) was significantly lower than that of patients ≥ 80% of the RBV dosage (112 of 189, 59.2%) and those ≥ 60% but < 80% of the RBV dosage (46 of 90, 51.1%) (both $P < 0.0001$), although no significant difference was found between those ≥ 80% of the RBV dosage and those ≥ 60% but < 80% of the dosage. In genotype 2, neither a dosage reduction of peg-IFN nor RBV significantly influenced SVR.

An analysis of the association between SVR and the total combined dosage of peg-IFN alpha-2b plus RBV showed that patients with a higher total combined dosage of the combination treatment had a significantly higher rate of SVR than those with a lower dosage for genotype 1 patients only, although no significant difference was found in genotype 2 (Fig. 4). In genotype 1, the SVR rate of patients ≥ 80% of peg-IFN alpha-2b and ≥ 80% of RBV was significantly higher (78 of 122, 63.9%) than those without these combined dosages (171 of 464, 36.8%) ($P < 0.0001$). Moreover, the SVR rate of patients ≥ 80% of peg-IFN alpha-2b and ≥ 60% of RBV was significantly higher (116 of 187, 62.0%) than those without these dosages (133 of 399, 33.3%) ($P < 0.0001$). However, in genotype 2, neither a dosage reduction of peg-IFN nor RBV significantly influenced SVR.

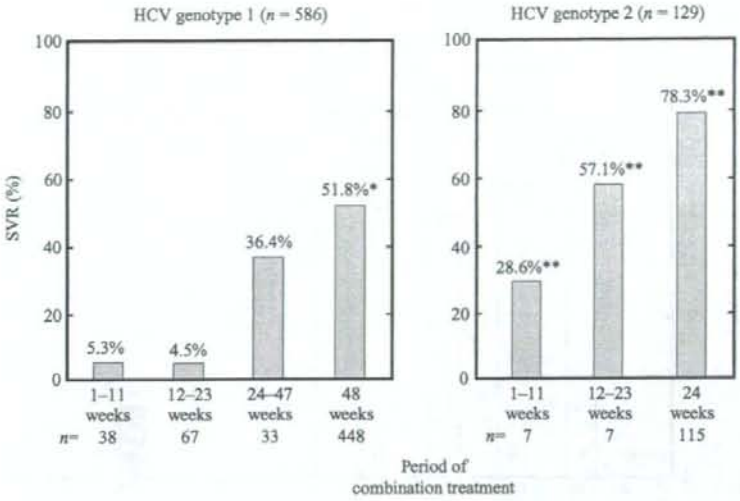

Figure 1 Sustained virological response (SVR) rates classified by length of pegylated interferon-alpha-2b (peg-IFN alpha-2b) plus ribavirin (RBV) combination treatment and by hepatitis C virus (HCV) genotype: An intention-to-treat analysis.

Analysis of EVR and the first 12-week adherence

An EVR was significantly higher in patients with genotype 2 (119 of 129, 92.2%) than in those with genotype 1 (307 of 586, 52.3%) ($P < 0.0001$). An analysis of the association between SVR and EVR showed that patients with EVR had a significantly higher rate of SVR than did patients without EVR for both genotypes 1 and 2: 220 of 309 (71.1%) versus 29 of 277 (10.4%) in genotype 1, and 96 of 119 (80.6%) versus none of 10 (0%) in genotype 2 (all $P < 0.0001$).

An analysis of the association between EVR and the first 12-week combined dosage of peg-IFN alpha-2b plus RBV showed that patients with a higher total combined dosage of the combination treatment had a significantly higher rate of SVR than those with a lower dosage for genotype 1 patients only, although no significant difference was found in genotype 2 (Fig. 5). In genotype 1, the EVR rate of patients ≥ 80% of peg-IFN alpha-2b and ≥ 80% of RBV was significantly higher (217 of 357, 60.7%) than those without these dosages (92 of 229, 40.1%) ($P < 0.0001$). Moreover, the SVR rate of patients ≥ 80% of peg-IFN alpha-2b and ≥ 60% of RBV was significantly higher (262 of 445, 58.8%) than those without these dosages (47 of 141, 33.3%) ($P < 0.0001$). However, in genotype 2, neither a dosage reduction of peg-IFN nor RBV influenced EVR.

Discussion

To the best of our knowledge, no reports have been written on the efficacy and safety of peg-IFN alpha-2b plus RBV treatment for a large number of Japanese HCV patients. The present study by intention-to-treat analysis included over 700 Japanese patients with chronic hepatitis C, a sufficient number to provide a meaningful statistical analysis and to be of interest to clinical physicians. Our findings show that in peg-IFN alpha-2b plus RBV treatment for chronic hepatitis C it is important to complete the target treatment duration and to use the full dosage to achieve virological efficacy.

A recent study showed Asian patients with chronic hepatitis C were more likely to achieve an SVR by treatment with peg-IFN alpha-2a and RBV than were Caucasian patients, suggesting a genetic influence on the antiviral response.[16] A significant difference between Asian and Caucasian patients with genotype 1 infections (65% and 36%) was also reported. However, the study included only 52 Asian patients and had no analysis concerning dosage of peg-IFN and RBV. Because our study included a large number of Japanese patients and an analysis of the complete combination treatment and the dosage of peg-IFN alpha and RBV, the present study provides for meaningful statistical analysis.

Our analysis showed that the discontinuation of RBV was significantly associated with a marked decline in SVR. We also showed that a < 60% reduction of the total dosage was associated with a poor outcome. Several adverse reactions are strongly associated with RBV. One of the most significant problems is hemolytic, especially anemia.[14] Most patients with anemia have general fatigue. Careful administration is necessary for patients > 60 years old, female patients, and patients receiving an RBV dosage by bodyweight of ≥ 12 mg/kg.[24] In fact, most of our patients who required a reduction in the total dosage or who discontinued RBV had anemia or fatigue. Also, discontinuation in this study was frequently found in patients aged ≥ 65 years. In Japan, many older patients with chronic hepatitis C are candidates for antiviral treatment, different from other countries. It is important to reduce the dosage of RBV at an early a stage as possible to allow the safe continuation of the combination treatment, as shown by data that a reduction of up to 60% of the total dosage of RBV does not appear to adversely influence SVR in Japanese patients.

The duration and dose of antiviral treatment are the most important factors influencing treatment outcome, especially in

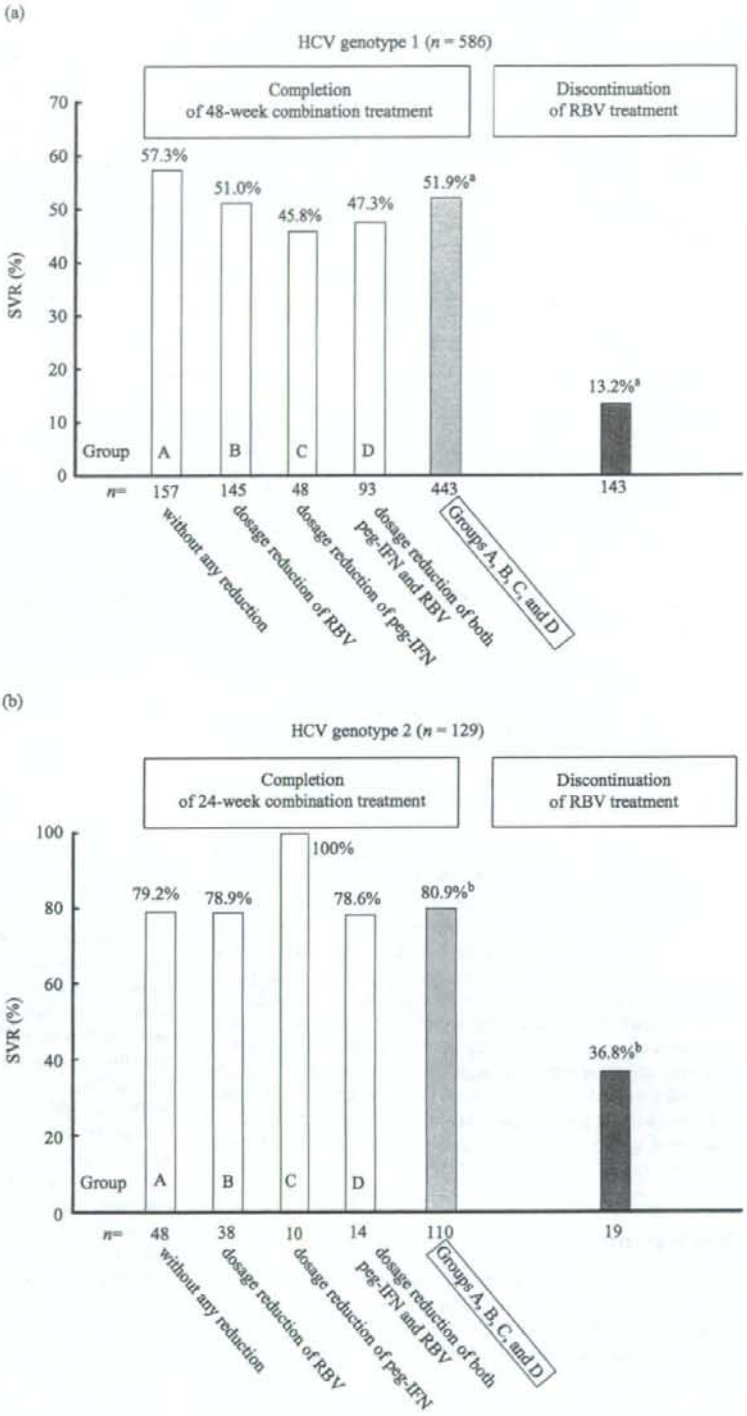

Figure 2 Sustained virological response (SVR) rates classified by continuation, reduction of the dosage, discontinuation of pegylated interferon-alpha-2b (peg-IFN alpha-2b) plus ribavirin (RBV) treatment, and hepatitis C virus (HCV) genotype: An intention-to-treat analysis (Fig. 2a for genotype 1 and Fig. 2b for genotype 2). The following groups A, B, C, and D consisted of patients who completed their scheduled combination treatment (48 weeks for genotype 1 patients [$n = 443$] and 24 weeks for genotype 2 patients [$n = 110$]) and patients who discontinued RBV treatment (genotype 1 patients [$n = 143$] and genotype 2 patients [$n = 19$]). Group A patients well tolerated the combination treatment with peg-IFN alpha-2b and RBV without any reduction in the target dosage of either drug; Group B patients completed the combination treatment and had no reduction of peg-IFN alpha-2b dose, but needed a reduction of the RBV target dosage; Group C patients completed the combination treatment and had no reduction of RBV dosage, but needed a reduction of the target dosage of peg-IFN alpha-2b; Group D patients completed the combination treatment, but needed a reduction of the target dosage of both peg-IFN alpha-2b and RBV. 'a' and 'b' indicate significant differences between completion of the full combination treatment and discontinuation of RBV treatment ($P < 0.0001$ and $P = 0.0002$, respectively).

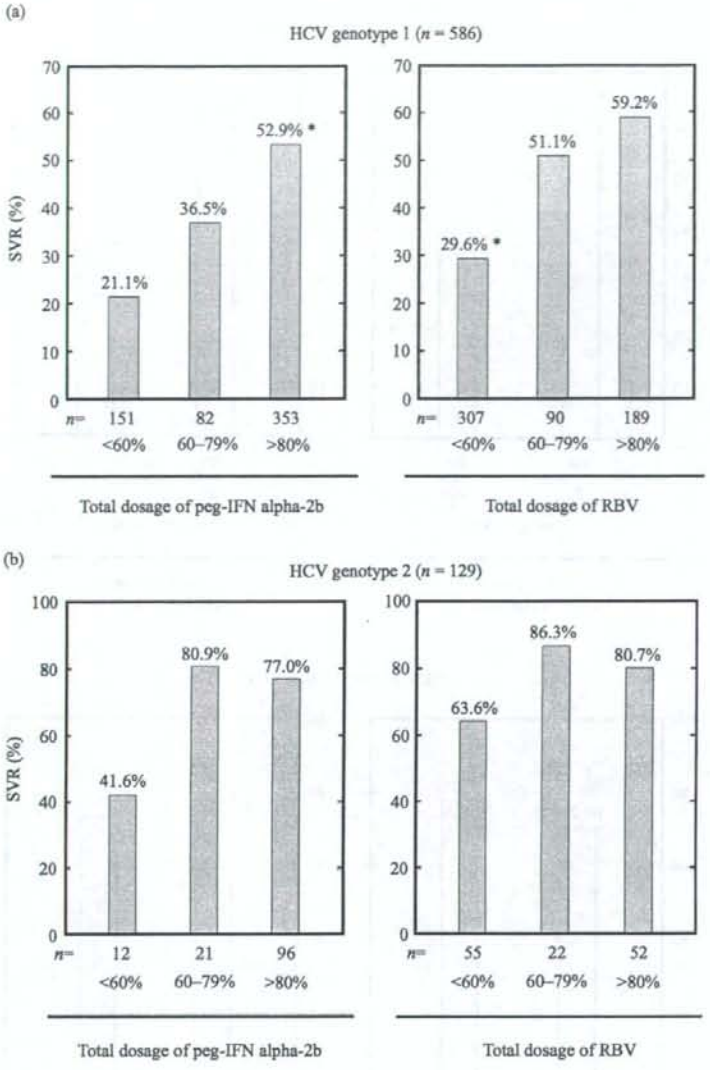

Figure 3 Sustained virological response (SVR) rates classified by percentage of total dosage of pegylated interferon-alpha2b (peg-IFN alpha-2b) plus ribavirin (RBV) treatment and by hepatitis C virus (HCV) genotype: An intention-to-treat analysis (Fig. 3a for genotype 1 and Fig. 3b for genotype 2). *indicates a significant difference between the groups.

HCV genotype 1-infected patients.[25,26] Shiffman and colleagues reported that reducing the total dose of peg-IFN alpha-2a to < 80% within the first 20 weeks of therapy significantly reduced SVR, but reducing the dose of RBV appeared to have little impact on SVR.[25] For our patients with genotype 1, the treatment period and total dosage were important to gaining SVR with peg-IFN alpha-2b plus RBV treatment. The 48-week combination treatment is the minimum requirement for SVR by these patients. Moreover, it is necessary to give ≥ 80% of the target dosage of peg-IFN alpha-2b (suitable for the weekly ≥ 0.9–1.2 μg/kg) and ≥ 60% of the target RBV (suitable for the daily 6–8 mg/kg) throughout the treatment.

Our previous report showed that a 24-week non-peg-IFN alpha plus RBV treatment regimen produced a high rate of SVR in Japanese genotype 2-infected patients.[19] The 24-week peg-IFN alpha-2b plus RBV treatment regimen used in the present study also demonstrated a remarkable rate of SVR (74.4%) for genotype 2 patients, as expected. This can be explained by the fact that genotype 2 patients have an extremely high rate of EVR, over 80%, with this combination treatment. Another important finding was that the total dosages of peg-IFN alpha-2b and RBV during the treatment for genotype 2 patients did not significantly influence SVR, although a dosage < 60% of the target resulted in a lower rate of SVR than a dosage ≥ 60%, without

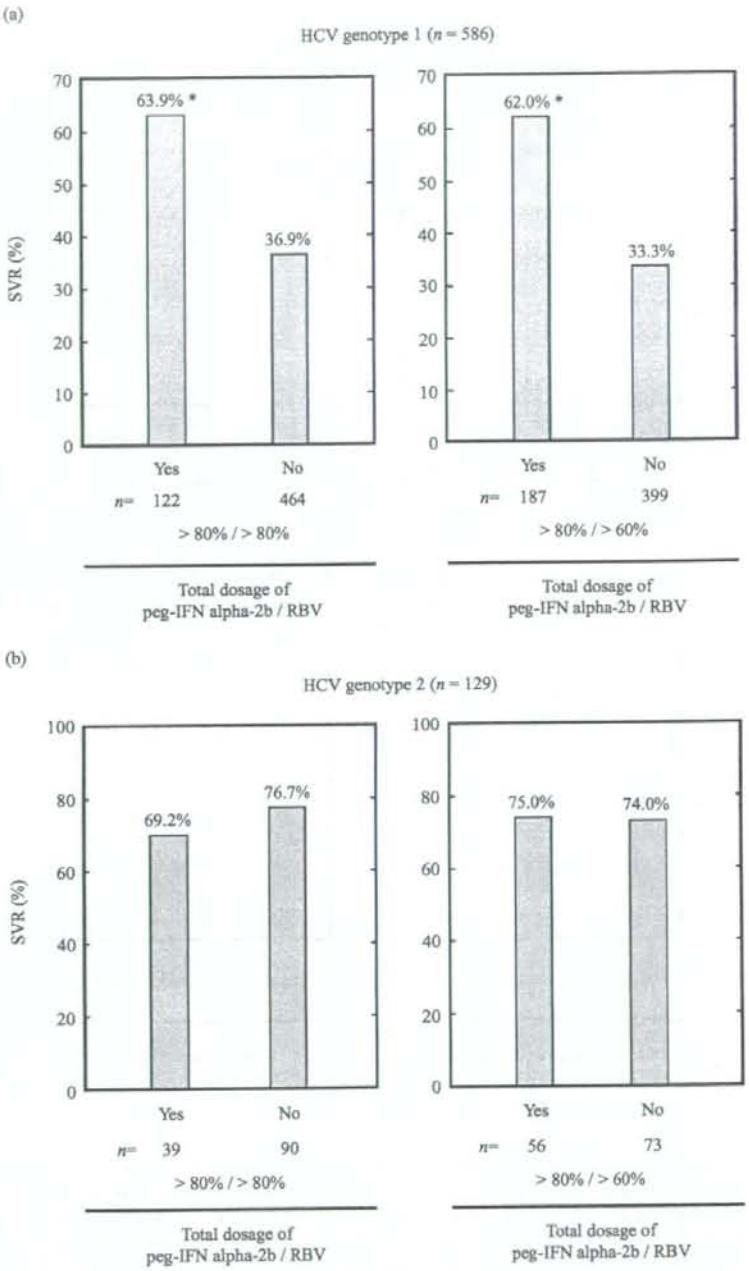

Figure 4 Sustained virological response (SVR) rates classified by percentage of total combined dosage of pegylated interferon alpha-2b (peg-IFN alpha-2b) plus ribavirin (RBV) treatment and by hepatitis C virus (HCV) genotype: An intention-to-treat analysis (Fig. 4a for genotype 1 and Fig. 4b for genotype 2). *indicates a significant difference between the groups.

significant difference. These findings suggest that the target dosage can be reduced for genotype 2 patients to avoid the adverse effects such as general fatigue, depression, and anemia and that the 24-week combination treatment can still be successfully completed.

An EVR, a virological clearance by antiviral treatment in the initial 12 weeks, is significantly related with sustained response.[27] The present study also showed that the first 12-week combined dosage was significantly related with EVR in both genotype 1 and 2 patients, leading to the attainment of an SVR.

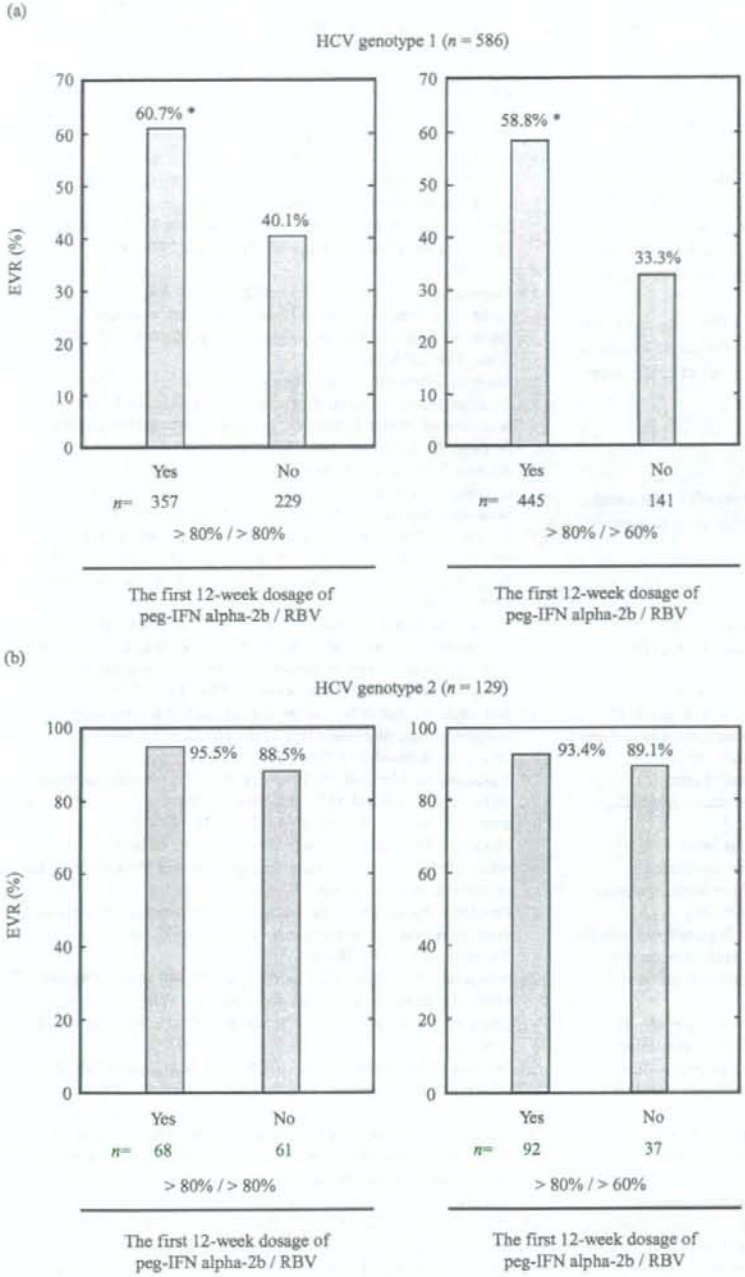

Figure 5 Early virological response (EVR) rates classified by percentage of the first 12-week combined dosage of pegylated interferon alpha-2b (peg-IFN alpha-2b) plus ribavirin (RBV) treatment and by hepatitis C virus (HCV) genotype: An intention-to-treat analysis (Fig. 5a for genotype 1 and Fig. 5b for genotype 2). *indicates a significant difference between the groups.

Because of the impact of medical adherence during the first 12-week dosage on EVR, it is important to continue the dosage from the early stage to the target period in peg-IFN alpha-2b plus RBV treatment.

Since the introduction of peg-IFN alpha plus RBV combination regimen, the treatment of chronic hepatitis C has dramatically improved over the past decade and can cure a significant proportion of the patients.[5,6] However, the combination treatment has its

limitations, especially for HCV genotype 1 patients. Although the limited efficacy and adverse effects necessitate the development of new therapeutics approaches, we must acknowledge the current situation in which many older Japanese patients with chronic hepatitis C are candidates for antiviral treatment. Therefore, a key to solving the problem is managing antiviral treatment for these older patients. Recent analysis suggests that using erythropoietic agents (epoetin and dartbepoetin) for the reduction of anemia may not be cost-effective for the majority of patients.[28] A new RBV analog, viramidine, is reported to be associated with a lower incidence of anemia than RBV (4% *vs* 27%),[29] and, if proven effective, may eventually be substituted for RBV in combination with peg-IFN alpha for patients with chronic hepatitis C.

In conclusion, in peg-IFN alpha-2b plus RBV treatment for chronic hepatitis C, it is important to complete the target duration and reach the target dosage to achieve virological efficacy, especially for genotype 1 patients.

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Appendix I

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薬剤師のための

感染制御標準テキスト

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じほう

2-2

院内で問題となる微生物と感染症
③ ウイルス感染症

ポイント

①血液由来ウイルスとしてはB型肝炎ウイルス（HBV），C型肝炎ウイルス（HCV），ヒト免疫不全ウイルス（HIV）が重要である。
②HBVは乳幼児期に感染すると持続感染が成立し，肝硬変，肝がんへと進行するが，成人で感染した場合は持続感染が成立しにくい。
③HCVは成人でも感染すると60～80%が持続感染となり，肝硬変，肝がんへと進行する。
④HIV感染症ではウイルス量とCD4陽性リンパ球数が臨床的に重要である。
⑤HIV感染症ではCD4陽性リンパ球数が200個／mm^3以下になると，種々の日和見感染症を併発する。
⑥A型インフルエンザ・ウイルスはウイルス表面のHAタンパクとNAタンパクの組み合わせにより流行が起こる。
⑦高病原性鳥インフルエンザ（H5N1）がヒトに感染しやすいように変異すると，大流行の可能性がある。
⑧ノロウイルスは感染力がきわめて強い。
⑨ワクチンによる麻疹，風疹抗体は終生免疫ではない。
⑩病院感染対策としては，血液由来ウイルス感染に対しては標準予防策で，呼吸器ウイルス感染症および発疹ウイルス感染症に対しては飛沫感染対策あるいは飛沫核感染（空気）対策で，消化器ウイルス感染症に対しては接触感染対策をとる。

1. はじめに

ウイルス感染症の診断が容易になった現在，その病院感染対策は重要となってきている。ウイルスは感染性が強いため病院感染対策が不必要なウイルス感染症は皆無といっても過言ではない。しかし，すべてのウイルス感染症について述べることは困難であるため，わが国で病院感染対策上問題となるウイルス感染症について述べる。

2. 血液由来ウイルス感染症

血液由来ウイルス（blood borne virus）は血液に寄生し，血液，体液などを介して

ほとんど非経口的に感染するウイルスで，ウイルスに持続的に感染しているキャリアという状態があり，症状がまったくない無症候性キャリアも存在している。血液由来ウイルスとして病院感染で問題になるのは，B型肝炎ウイルス（HBV），C型肝炎ウイルス（HCV）およびヒト免疫不全ウイルス（HIV）である。

成人T細胞白血病ウイルス（HTLV-1）も血液由来ウイルスであるが，発症まで感染後約50年を要すること，さらにはわが国では九州地区に偏在していることも考慮し，ここでは省略する。なお，血液由来ウイルスに対する病院感染対策は標準予防策で対応する。

(1) B型肝炎ウイルス（HBV）

1）感染経路と疫学

HBVの感染経路としては，輸血などの医療行為だけでなく性行為を含むヒトとヒトとの密接な接触でも感染する。HBV感染様式には持続感染と一過性感染がある。免疫機能の未熟な3歳以下の乳幼児がHBVに感染すると，高率に持続感染に移行する可能性があるが[1]，成人では持続感染に移行することはない。

HBVのgenotypeとして，わが国ではB型およびC型が主流で，B型のキャリアはC型に比較して，ウイルスの増殖が早期に低下しており，予後が良いものと考えられている[2]。近年，欧米で主流のgenotype A型が男性同性愛者を中心に増加しているが，このA型に感染した場合は，成人でも持続感染に移行することが指摘されている。

2）臨床経過および診断

持続感染者の15～40%が慢性肝炎，肝硬変，肝がんへ進行する。その間血中のHBs抗原は持続して検出されるが，HBVが野生型からHBe抗原を産生しない変異型に置き換わると，感染初期に検出されたHBe抗原は消失し，HBe抗体が検出されるようになる。一部の持続感染者ではHBs抗原が消失し，HBs抗体が出現する[3,4]。この抗体は感染防御抗体で，HBワクチンにより獲得することもできるので，医療従事者として知っていなければならないHBVマーカーである。HBc抗体はHBVに感染した例では感染初期より終始陽性で，陰性となることはない。

B型急性肝炎では，一定の潜伏期の後に，黄疸，発熱，消化器症状，倦怠感などが発症し，血液生化学的には，AST，ALT，LDHが著明に上昇し，総ビリルビンも上昇することが多い。

3）治療法

B型急性肝炎は，特別な治療を要さず，自然にHBVは排除されて完治し，慢性化することはない。臨床上問題となるのはHBe抗原を産生しない変異型HBVに感染した場合の劇症肝炎である[5]。予後不良であるが，近年，肝移植が良好な成績を収めている。

B型慢性肝炎に対する治療としては，インターフェロン（IFN）あるいは核酸誘導

体（ラミブジン，アデフォビル，エンテカビル）が投与される。これらの治療により患者の60～80%はウイルス血症および肝機能改善がみられる[6]。

4）感染対策

血液中に含まれているウイルス量が多いこと，および非生物環境でも安定していることから，血液由来ウイルスのなかでは，HBVの感染力が最も強い。血液の曝露を受けやすい職種ではHBVに対するHBワクチンの接種が推奨される[7]。曝露後の対策としては，曝露後48時間以内のHBグロブリン投与とHBワクチン接種である。

(2) C型肝炎ウイルス（HCV）

1）感染経路と疫学

わが国での主な感染経路は輸血だけでなく，注射器などがディスポーザブルでなかった時代の医療行為であったと推定されている[8]。HBVと異なる点は，成人でも感染すると60～80%は持続感染となり，その大部分が慢性肝炎，肝硬変，肝がんと進行する[9]。わが国の肝がんの70%はHCV感染者である[10]。

2）臨床経過および診断

HCV感染者ではHCV抗体が検出されるが，血中のHCV RNAの検出が，現在感染していることの証明となる。HCV感染者のgenotypeは1b型が80%を占めており，次いで2a型，2b型である[8,11]。

C型急性肝炎の症状，経過は他のウイルス肝炎とほぼ同様であるが，一般にはB型急性肝炎に比べ軽度で，劇症化はまれである。

3）治療法

慢性肝炎にはIFN療法が行われるが，現在は週1回の注射で血中濃度が保たれるペグ化されたIFN-αとリバビリンとの併用療法が主流となっている[12]。IFN療法は肝機能の改善だけでなく，ウイルスの排除[13]，さらには肝がん発症の防止効果も報告されている[14]。低HCV RNA量，genotype 2型がIFNの有効因子である。

4）感染対策

曝露後の経過観察と感染成立後のIFN療法である。IFN療法は感染成立後早期にしたほうが有効率が高い[15]。

(3) ヒト免疫不全ウイルス（human immunodeficiency virus：HIV）

1）感染経路と疫学

HIV感染者は世界的には4,000万人を超えているが，わが国でも年々増加傾向を示し累計1万人を超え，年間1,000人以上が新規登録されている。わが国では血液製剤による感染者や同性愛間性行為による感染者が多いが，世界的にみると異性間性行為による感染者が60～70%，同性間性行為によるものが5～10%で，血液によるものが3～5%，薬物乱用の注射によるものが5～10%，母子感染によるものが5～10%とされている。

2）臨床経過と診断

HIV に感染すると数年後に HIV RNA 量が増加しはじめ，CD4 陽性リンパ球数が急速に減少し，日和見感染症などを併発し後天性免疫不全症候群（acquired immunodeficiency syndrome：AIDS）となる。

HIV の感染 2 週～2 カ月後の初期では，伝染性単核球症様症状を 2～3 週間呈することがあるが[16]，無症状の場合もある。慢性期に移行すると無症候性の時期にもリンパ組織では濾胞樹状細胞などを中心に HIV が大量に存在し，毎日約 1 億個のウイルスが絶え間なく複製されている。HIV 量が多いと CD4 陽性リンパ球数の減少が早くなるのみならず，逆転写される量も多いため変異の出現も多くなり，病原性（virulence）の高い変異株や薬剤耐性の変異株が出現し，病状が進行しやすい。

CD4 陽性リンパ球数はその時点の免疫状態を示すのに対し，血中 HIV RNA 量はその後の病状進行速度の指標といえる。治療の開始時期，治療効果の判定，治療薬変更時期の判断など臨床上の重要な判断はほとんど，これら 2 つの指標によってなされる[17]。

CD4 陽性リンパ球数が 200～350 個／mm^3 では，持続性全身性リンパ節腫脹，発熱，下痢，口腔カンジダ症，体重減少などを伴う AIDS 関連症候群を呈する時期に入る。CD4 陽性リンパ球数が 200 個／mm^3 以下になると，カリニ肺炎その他のいわゆる AIDS の指標疾患が出現しやすくなる。

HIV 感染の確実な診断は，抗体検査で通常は ELISA 法および PA 法でスクリーニングし，抗体陽性の場合と，感染後間もない場合（window period）には PCR 法にて HIV RNA の検出を試みる必要がある。

3）治療法

抗 HIV 薬には，基本的にはヌクレオシド系の逆転写酵素阻害薬，非ヌクレオシド系逆転写酵素阻害薬およびプロテアーゼ阻害薬の 3 種類がある。単剤では耐性ウイルスが出現し，1～2 年以内に効果が失われることが多いため，上述した 3 種類の抗 HIV 薬の組み合わせによる多剤併用療法（highly active antiretroviral therapy：HAART）が行われ，良好な成績が得られている[17]。

4）感染対策

感染成立の可能性が考えられる曝露の場合，ただちに逆転写酵素阻害薬とプロテアーゼ阻害薬の 1 カ月間の予防投与を行う。

3. 呼吸器ウイルス感染症

乳幼児に肺炎を起こす RS ウイルス感染症なども重要であるが，ここではインフルエンザについて述べる。

(1) インフルエンザ

1）ウイルスの性状と疫学

病原性が強いインフルエンザウイルスは A 型と B 型である。ウイルスのエンベロ

ープには2種類のスパイク，ヘマグルチニン（hemagglutinin：HA）およびノイラミニダーゼ（neuraminidase：NA）が突き出ており，M2と呼ばれるタンパクも膜に存在する。A型は2種類のスパイクのHAタンパクには1～15およびNAタンパクには1～9の亜型が存在し，その組み合わせで流行が起こっている。また，すべてのA型インフルエンザの起源はカモなどの水禽類と考えられている。

2）感染成立の機序

HAタンパクがプロテアーゼ（タンパク分解酵素）によって，特定の1カ所で2つのタンパクサブユニット（HA1とHA2）とに分解されることにより，宿主細胞に感染が成立する。増殖した感染細胞内ウイルスは，NAタンパクの酵素作用により感染細胞から遊離する。

3）症状および臨床経過

インフルエンザに感染すると，1～3日の潜伏期を経て，悪寒戦慄，38℃以上の発熱，頭痛，関節痛，全身倦怠感などの症状で発症し，続いて咳や鼻水などの呼吸器症状も目立ってくる。発症後3～4日間がウイルス排泄のピークで，他者への感染源となる。高齢者では，しばしば発熱や自覚症状は軽度であるが，傾眠傾向を示したり，肺炎を合併して死亡する例もみられる[18]。

4）診断および治療

診断は簡便な迅速診断キットが用いられ[19]，治療についてはノイラミニダーゼ阻害薬およびアマンタジンが使用されている。ノイラミニダーゼ阻害薬は，A型およびB型のいずれにも有効であるが，小児での精神症状が問題となっている。アマンタジンはM2タンパクの作用を阻害しウイルスの増殖を抑制し，A型にしか効果がない。いずれの薬剤も予防効果が認められている[20]。

5）感染対策

飛沫感染予防策であるが，飛沫核（空気）感染予防策の必要性も考えられる。現在のところ，インフルエンザワクチンの接種が最も効果があるとされている。特に，医療従事者は患者からの感染だけでなく，患者への感染事例もあるため，ワクチン接種は必須と考えられる。

6）高病原性鳥インフルエンザ（H5N1）

1997年に香港でニワトリからヒトに小流行がみられたインフルエンザ（H5N1）が，2004年からベトナム，タイ，インドネシアで流行している。ニワトリだけでなく，ニワトリからヒトへ，さらにはヒトからヒトへの感染も認められ，死亡率が高いこともあり重大な問題となっている[21]。ワクチンの製造は，ニワトリの受精卵に感染させるウイルスが高病原性のため，受精卵が死滅し困難となっている。したがって，今のところ予防法としてはマスクの装着が重要であるが，市販されているマスクの大部分はウイルスを防御できない。確実な感染防御効果を得るためには，N95あるいはFSCマスクなどの装着が必要である[22]。治療に関してはノイラミニダーゼ阻害薬の早期投与で効果が確認されている。

いずれにしろ，このウイルスがヒトからヒトへ感染している事実を考えると，人間社会での大流行に注意する必要がある。

4. 消化器系ウイルス感染症

消化器系ウイルス感染症は病院感染としてしばしば問題となることが多い。原因ウイルスとしては，アデノウイルス，エンテロウイルス，ロタウイルス，ノロウイルスなどがあるが，その確定診断法は便からのウイルス分離あるいはPCR法によるしかない。そのため，その病院感染対策としては患者の症状を目安とせざるを得ないことが多い。いずれにしても，病院感染対策としては接触感染予防策を行わなければならない。

ここでは感染力が強いことから，注目されているノロウイルス感染症について述べる。

感染様式は糞口感染である。ヒトからヒトへの感染以外に，汚染された飲料水や食物（生カキが最も多い）からの感染があり，ウイルス性食中毒の集団発生の原因となる。

臨床症状としては，発熱，嘔吐，下痢，腹痛で，特に嘔吐の頻度が高い傾向にある。ウイルスは糞便中に1週間は排泄され感染源となりうる。ノロウイルス胃腸炎は通年性にみられるが，わが国における好発季節は11月から1月にピークがある[23]。

治療としては，輸液などにより，下痢による脱水症状の改善を図る。近年，高齢者の死亡報告もあり注意を要する。

5. 発疹性ウイルス感染症

これらのウイルス感染症は，主として小児期の感染症であるが，若年成人での感染も増加しており，臨床上，病院感染対策上重要な問題となっている。

(1) 麻疹

麻疹は感染すると10～12日の潜伏期間後に，発熱，結膜充血，かぜ症状などのカタル期を経て，全身性に発疹が出現し，10日前後で回復する。成人麻疹は肺炎などが合併し，一過性の強い免疫抑制状態になり重症化することがある[24]。

わが国での問題は，この重症化する成人麻疹が増加していることである。この理由としては，病後免疫およびワクチン接種後免疫は麻疹の再感染を受け，不顕性感染を繰り返すことで自然追加免疫の効果が得られ，結果的に免疫が長期間持続している[25]。しかし，近年，麻疹の流行が小規模になり，不顕性感染の機会が減少するため，病後免疫もワクチン接種後の免疫も減弱する。このために，再感染を受けたとき発病を免れることができない成人が増加しているためと考えられる。特に，ワクチンによる獲得免疫は終生免疫ではないため注意を要する。

病院感染対策としては空気感染予防策である。