DOI: 10.2169/internalmedicine.46.6122

Table 1. Facial Lipoatrophy Severity Scale

Grade I: mild and focalized facial lipoatrophy
Grade II: deeper and longer atrophy, with facial muscles beginning show through
Grade III: atrophic lesion even deeper and wider, with the muscles clearly showing
Grade IV: lipoatrophy covers wide area, extending toward the eye sockets, and the facial skin lies directly on the muscles

Table 2. Characteristics of Patients at Entry

Patients (n)	25
Male	21
Female	4
Age (years)	38.6 (24-55)
Duration of antiretroviral treatment (years, mean, SD)	4.79 (1.61)
Mean CD4 (cells/mm^3) (mean, SD)	468.4 (202.2)
Number of patients with viral load less than 50 copies/ml	22 (88%)

3) have not been treated with rhGH or other anabolic steroid in the past 6 months, 4) fasting blood glucose <126 mg/dl (9), 5) no obvious current opportunistic infection.

The number of participants was set according to the conditions of the pilot study, quality control of safety and monitoring, and the amount of rhGH provided by the manufacturer; 25 patients, 21 males and 4 females, aged between 24 and 54 years were enrolled the study. The average duration of antiretroviral treatment was 4.79 years, and 22 patients were with undetectable (less than 50 copies/ml) viral load, the average CD4 was 468.4 cells/mm^3 (468.4+/- 202.2) (Table 2).

Procedures and Statistical Analysis

rhGH (5 mg) was given subcutaneously every other day for 6 months. After the completion of the rhGH injection, patients were followed up for 6 months. The observation period was a total of 12 months. Antiretroviral treatment was continued throughout the study. rhGH was provided by Serono Japan Co., Ltd.

The primary endpoint was the change in the soft tissue thickness of the face. All patients had computed tomography (CT) of the face at the level of maxillary sinus, zygomatic arch and mandibular ramus at months 0, 3, 6 and 12 (10). Preliminary, interobserver variability was evaluated. CT of the face was performed and the soft tissue thickness in each slice was measured by two independent radiologists. Kappa value was 0.754, which was considered acceptable agreement. Upon the result, the facial soft tissue in all slices was measured by one radiologist. Analysis of variance was used as the statistical method. Multiple comparison of Dunnett-Hsu analysis was used to test the difference between each soft tissue thickness in CT in comparison with their baseline.

The secondary endpoint includes body composition assessed by body mass index, circumflex of limbs and percentage of body fat, blood test with lipid profile, glucose and liver function test, CD4 and viral load which were measured at each visit at months 0, 3, 6 and 12. Patients were also asked to complete questionnaires on their quality of life. Facial photographs were taken at each visit.

The Ethics Committee of the International Medical Center of Japan approved the study. All participants were informed about the study and gave written consent prior to the participation.

Result

Of the 25 participants, one patient had severe diarrhea within 1 month and withdrew from the study. 24 completed the study, however, the digital CT data of 4 patients was partially lost due to technical error. Therefore, the CT scans of 20 participants were analyzed.

The sum of bilateral facial soft tissue at the level of zygomatics at months 0, 3, 6, 12 were 7.23 mm; 8.59 mm, 8.35 mm and 8.60 mm, respectively (Fig. 1). Dunnett-Hsu analysis of adjusted multiple comparison of least squares means found significant improvement of soft tissue thickness from the baseline in the month 3 ($p=0.009$) and month 12 ($p=0.021$). Even after the completion of rhGH injection at month 6, the soft tissue at the level of zygomatics showed no significant decrease for the follow-up period.

There was no significant change in the circumference of arm and thigh, and liver function, CD4 nor HIV viral load during the study. BMI and lipid profile also showed no change except for glucose between months 0 and 6, both of which were within the normal limit (Table 3).

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Table 3. Change of Laboratory Characteristics

	month 0	month 3	month 6	month 12	p (month 0 to 6)	p (month 0 to 12)
BMI (mean, (SD))	20.8 (2.6)	21.3(2.3)	21.1 (2.9)	21.5 (2.8)	0.188	0.009
Glucose (mean, (SD))	89.8 (15.5)	96.5 (17.7)	101.5 (17.9)	92.6 (16.3)	< 0.0005	0.592
Triglyceride (mean, (SD))	288.5 (146.5)	299.0 (157.9)	247.3 (158.5)	319.3 (254.6)	0.211	0.593
Total Cholesterol (mean, (SD))	201 (45.2)	199.9 (48.0)	191.2 (41.5)	195.5 (16.3)	0.114	0.431

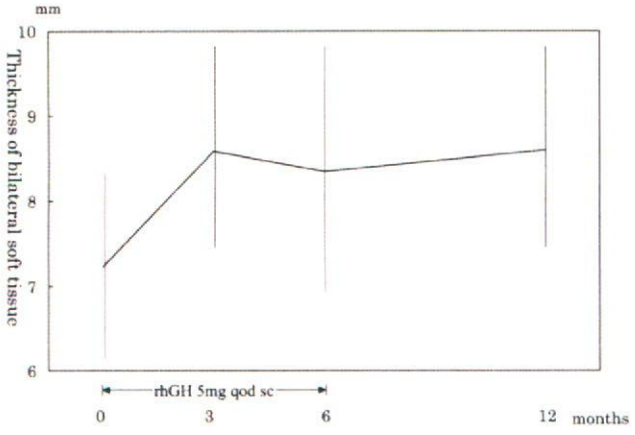

Figure 1. Thickness of bilateral soft tissue at the level of zygomatics, 95% CIs.

The quality of life questionnaire revealed that 19 of 25 patients had felt some improvement in their appearance and they were satisfied with the results.

Several adverse events were noted during the study. One patient withdrew due to severe diarrhea. His symptoms gradually subsided after the cessation of rhGH. Ten patients experienced transient self-limited mild arthralgia or muscle ache, 3 male patients had mild mastalgia or enlargement of breast tissue, and one had right hand numbness. All symptoms have resolved after the completion of the rhGH.

Discussion

Facial lipoatrophy is one of the long-term adverse effects of HAART for which standard treatment is not yet found and it severely interferes with the patient's quality of life. Several studies using surgical intervention have been reported to show limited transient effects (8). Some studies have reported the effect of growth hormone for lipoatrophy or lipodystrophy in relation to the total body composition or glucose metabolism (3-6, 11, 12). However, there has been no report of rhGH effect focusing on facial lipoatrophy. This prospective study was designed as a single arm pilot study to focus on the change of facial soft tissue thickness and the maintenance effect with the use and after the cessation of rhGH. All of the participants were followed and evaluated by a single institute, which had the benefit of close clinical monitoring for patient safety and quality assurance of the study. The soft tissue at the zygomatics showed significant improvement of lipoatrophy in month 3 with rhGH and in the observation period without rhGH in month 12. The effect was sustained for 6 months after the cessation of rhGH. This CT- based evaluation method is accurate and reproducible. In particular, the Kappa value of 0.754 showed that the interobserver variability is minimal.

Considering the fact that many patients who have been on long-term antiretroviral treatment in the era of HAART suffer from lipoatrophy (6, 7), this study proved that rhGH has a significant and sustained effect on the improvement of facial lipoatrophy.

Other clinical parameters, including BMI, liver function test, lipid profile, serum glucose, viral load and CD4 showed no significant change. Although severe diarrhea had led a patient to withdraw from the study, other side effects (arthralgia, myalgia, mastalgia and hand numbness) were self-limited and transient. Upon consideration of these results, rhGH can be considered relatively safe to use.

While the standard use of rhGH is 5 mg subcutouneously every day, several studies have shown that low-dose rhGH was effective in visceral adipose tissue and preventive of the change in glucose tolearanve or insulin sensitivity (11, 12). Our study protocol reduced the frequency to every other day with the standard dose, aiming to prevent changing glucose tolerance and to reduce the cost while expecting the maximal effect. The result showed that there was no significant change in glucose intolerance and lipid profile on rhGH. The outcome is quite encouraging.

A potential weakness of the study is the cost of rhGH. For this trial, rhGH was provided by the manufacturer. However, the total cost of rhGH of this study was about 37,000 USD for 6 months use for one patient. The national health insurance of Japan approves of rhGH only for the treatment of HIV-related wasting syndrome. None of the participants met the criteria at the entry of this study. The cost effectiveness of the use of rhGH for facial lipoatrophy will require further discussion.

Conclusion

rhGH is effective and relatively safe for moderate to severe facial lipoatrophy while it is in use and after the cessation. Patients were satisfied with the outcomes of subcutaneous injection of rhGH. The cost effectiveness of rhGH for facial lipoatrophy needs further discussion.

DOI: 10.2169/internalmedicine.46.6122

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Hepatology Research 2008; **38**: 310–314 doi: 10.1111/j.1872-034X.2007.00263.x

Short Communication

Prevalence of hepatitis B virus infection in Japanese patients with HIV

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Patients with HIV infection are frequently infected with hepatitis viruses, which are presently the major cause of mortality in HIV-infected patients after the widespread use of highly active antiretrovirus therapy. We previously reported that approximately 20% of HIV-positive Japanese patients were also infected with hepatitis C virus (HCV). Hepatitis B virus (HBV) infection may also be an impediment to a good course of treatment for HIV-infected patients, because of recurrent liver injuries and a common effectiveness of some anti-HIV drugs on HBV replication. However, the status of co-infection with HIV and HBV in Japan is unclear. We conducted a nationwide survey to determine the prevalence of HIV–HBV co-infection by distributing a questionnaire to the hospitals belonging to the HIV/AIDS Network of Japan. Among the 5998 patients reported to be HIV positive, 377 (6.4%) were positive for the hepatitis B surface antigen. Homosexual men accounted for two-thirds (70.8%) of the HIV–HBV co-infected patients, distinct from HIV–HCV co-infection in Japan in which most of the HIV–HCV co-infected patients were recipients of blood products. One-third of HIV–HBV co-infected patients had elevated serum alanine aminotransferase levels at least once during the 1-year observation period. In conclusion, some HIV-infected Japanese patients also have HBV infection and liver disease. A detailed analysis of the progression and activity of liver disease in co-infected patients is needed.

Key words: co-infection, hepatitis B, HIV, liver disease.

INTRODUCTION

HEPATITIS B VIRUS (HBV) infection is a major public health problem worldwide, along with hepatitis C virus (HCV) and HIV infections. In the USA, the estimated prevalence of HBV is less than 1%, but approximately 1 million people are persistently infected.[1] The prevalence of HIV in the USA is also <1%, and the virus is estimated to have infected approximately 800 000 people.[2] Because of the common transmission routes, that is, parenteral transmission routes, many people with HIV infection are also infected with HBV. Among the HIV-positive people in the USA, the prevalence of HBV co-infection is 6–14%.[1,2] Before the introduction of highly active antiretroviral therapy (HAART) in 1996, most patients with HIV infection died of HIV-associated opportunistic infections, such as *Pneumocystis jiroveci* pneumonia and cytomegaloviral infection. Since the widespread use of HAART, the mortality associated with HIV infection has declined. However, the reduction in mortality due to opportunistic infection, has left patients co-infected with HIV and hepatitis viruses faced with the menace of progressive liver diseases due to HBV infection,[3,4] in addition to HCV infection.[5]

HBV co-infection or superinfection of HIV-infected patients leads to several problematic situations. First, HBV infection tends to develop into persistent infection in HIV-infected patients,[1,6,7] which is a rare event in healthy adults, although it substantially depends on the genotype of HBV.[8] It results in the acceleration of the development of cirrhosis and eventually hepatocellular carcinoma. Second, some nucleoside reverse transcriptase inhibitors (NRTI) used in HAART also have

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Received 22 June 2007; revision 29 July 2007; accepted 31 July 2007.

inhibitory effects on the replication of HBV.[9–12] A careless administration or discontinuation of NRTI on HIV–HBV co-infected patients may cause reactivation and/or aggravation of hepatitis B. In addition, the administration of anti-HBV drugs in HIV–HBV co-infection may lead to the development of drug resistance.[11,12] Third, liver injury occurs more frequently in patients on HAART who are co-infected with HIV and HBV than those infected with HIV only.[9,10]

Importantly, co-infection with HIV and HCV increases the morbidity and mortality of HIV-infected patients in Japan,[13] where the prevalence of HIV infection is increasing linearly, and is exceptionally high among developed countries.[14] There are more than 14 000 HIV-positive people in Japan as of 2006, according to the AIDS National Survey in Japan,[14] and approximately 0.8 million chronic HBV carriers.[15] However, the prevalence of co-infection with HIV and HBV in Japan has not been clarified to date. Therefore, we conducted a nationwide study by distributing a postal mail-based questionnaire to the hospitals belonging to the HIV/AIDS Network of Japan.

PATIENTS AND METHODS

IN THE QUESTIONNAIRE, the following information was obtained from the hospitals regarding the number of patients who visited the hospitals at least once between January and December in 2006: (i) the number of HIV-positive patients; (ii) the number of hepatitis B surface antigen (HBsAg)-positive patients among (i); (iii) the number of patients among (ii) who were determined at least once to have a serum alanine aminotransferase (ALT) level higher than 100 IU/L; (iv) the number of HIV-positive patients that contracted HIV from blood products; (v) the number of HBsAg-positive patients among (iv), (vi) the number of patients among (v) who were determined at least once to have a serum ALT level higher than 100 IU/L; (vii) the number of HIV-positive patients among homosexual men, (viii) the number of HBsAg-positive patients among (vii), (ix) the number of patients among (viii) who were determined at least once to have a serum ALT level higher than 100 IU/L; (x) the number of HIV-positive patients that contracted HIV through intravenous drug use (xi) the number of HBsAg-positive patients among (x), (xii) the number of patients among (xi) who had at least one determination of a serum ALT level more than 100 IU/L; (xiii) the number of HIV-positive patients whose transmission routes were classified as "others"; (xiv) the number of HBsAg-positive patients among (xiii); and (xv) the number of patients among (xiv) who were determined at least once to have a serum ALT level higher than 100 IU/L.

The questionnaire was sent to the 372 hospitals belonging to the HIV/AIDS Network of Japan by mail. Answers were mostly returned by mail and in some cases by fax. The list of the hospitals in the HIV/AIDS Network of Japan can be viewed at http://www.acc.go.jp/mLhw/mLhw_frame.htm.

RESULTS

THE QUESTIONNAIRE WAS sent to all 372 hospitals that were on the list of the hospitals in the HIV/AIDS Network of Japan in January 2006. Two hundred and seven hospitals (55.6%) responded within the indicated period. In total, 5998 patients were reported to be HIV positive. The collection rate of 55.6% was higher than that (47.8%) for a questionnaire HIV–HCV co-infection study carried out in 2003.[15] It may appear rather low, particularly considering the number of reported HIV-positive people in 2006, which was approximately 14 000, according to the AIDS National Survey in Japan.[14] However, not all of the HIV-positive people were going to hospitals, and the answers to the questionnaire were obtained from most of the major hospitals in the HIV/AIDS Network in big cities around Japan. This suggests that not all, but a majority of HIV-positive Japanese patients were enrolled in the study.

Among the 5998 patients reported to be HIV positive, 377 (6.3%) patients were positive for HBsAg (Table 1). Of these 377 patients, 122 (32.4%) had elevated serum ALT levels at least one time during the 1-year observation period.

The HBV prevalence rates, when fractionated by the routes of transmission, were as follows: among the 508 HIV-positive patients who contracted HIV from blood products, such as unheated concentrated coagulation factors, only 30 (5.9%) were HBsAg positive, which shows a marked contrast to the prevalence of HCV in this cohort (Fig. 1).[16] Among the 23 intravenous drug users, three (13.0%) were HBsAg positive. Among the 3213 HIV-positive patients who were homosexual men, 267 (8.3%) were HBsAg positive. In the remaining 2254 patients who were HIV-positive and whose route of HIV transmission was classified as "others", most contracted HIV heterosexually. This number (2254) showed a substantial increase from the 1316 obtained in the questionnaire for the HIV–HCV co-infection study in 2003, while the total number of HIV-positive patients increased from 4877 to 5998.[16] Among these, 77 (3.4%)

Table 1 Prevalence rates of hepatitis B virus infection among HIV-positive patients

Routes of transmission	No. patients	HBsAg positive (% in HIV positive according to route)	ALT >100 IU/L (% in HBsAg positive according to route)
Blood products	508 (5.9%)	30 (40.0%)	12
Homosexual men	3213 (8.3%)	267 (32.2%)	86
Drug addicts	23 (13.0%)	3 (66.7%)	2
Others (heterosexual etc.)	2254 (3.4%)	77 (28.6%)	22
Total	5998	377 (6.3%)	122 (32.4%)

ALT, serum alanine aminotransferase; HBsAg, hepatitis B surface antigen.

were HBsAg positive. In terms of the route of HIV infection, 267 (70.8%) of the 377 patients were homosexual men among the HIV–HBV co-infected patients. This shows a contrast to the status of HIV–HCV co-infection, in which the majority of HIV–HCV co-infected Japanese patients contracted both viruses from blood products.[16]

There were one or more HIV-positive patients in 154 (74.4%) of the 207 hospitals in the HIV/AIDS Network of Japan (Table 2). Twenty four (11.6%) of 207 hospitals had 20–49 HIV-positive patients, and 16 (7.7%) hospitals had 50 or more HIV-positive patients. There were one or more patients who were co-infected with HIV and HBV in 64 (30.9%) of the 207 hospitals. There were 10 or more HIV–HBV co-infected patients in nine (4.3%) hospitals, all of which had 50 or more HIV-positive patients (Table 2). HIV–HBV co-infected patients were concentrated in specific hospitals in big cities around Japan. In particular, in the Kanto area, HIV–HBV co-infected patients were concentrated in the HIV/AIDS Network hospitals in the Tokyo city area.

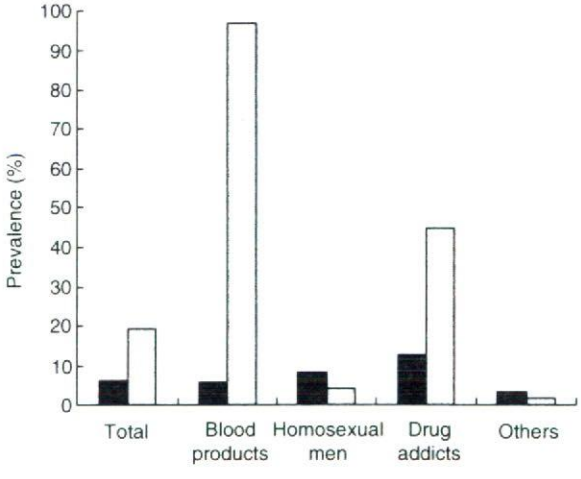

Figure 1 Prevalence rates of persistent hepatitis B virus and hepatitis C virus infections in the HIV-positive population sorted by the HIV risk group. (■), HBsAg, hepatitis B surface antigen; (□), anti-HCV, antibody to hepatitis C virus. *Prevalence rates of anti-HCV are obtained from Koike K *et al.*[16]

DISCUSSION

ALONG WITH THE increase in the number of HIV-infected patients in Japan, co-infection with HIV and hepatitis viruses has become a major medical issue. HBV infection of HIV-positive patients raises several difficult problems: HBV infection tends to develop into persistent infection, even in adults; some NRTI used in HAART also have inhibitory effects on the replication of HBV, the improper administration, or discontinuation of which may lead to drug resistance; and HIV–HBV co-infected patients on HAART have liver injuries more frequently than HIV-monoinfected patients. It is important to determine the status of HBV infection in HIV-positive patients.

According to the statistics of the Ministry of Health, Labor, and Welfare of Japan, the number of reported HIV-positive people was slightly over 14 000 in 2006.[14] In the present study, 6.4% of HIV-positive patients were positive for HBsAg, the most reliable marker for ongoing HBV infection. It might have been advantageous if

Table 2 Number of hospitals categorized according to the number of patients infected with HIV and those co-infected with HIV and hepatitis B virus (HBV)

No. HIV (+)/ HBV (+)	No. HIV(+)				
	0	1–19	20–49	50+	Total
0	53	76	13	1	143
1–9	0	38	11	6	55
10+	0	0	0	9	9
Total	53	114	24	16	207

serum HBV–DNA levels were determined, but unfortunately, HBV–DNA level determination was not a routine laboratory test in most hospitals. In addition, considering that the antibody to the hepatitis B core antigen might be the only marker of ongoing HBV infection in some immuno-compromised patients, it would also be advantageous if this viral marker were available. These issues should be investigated in future studies. Comments from hospitals to the questionnaire included one indicating that not all HIV-positive patients underwent a test for serum HBsAg, suggesting the actual prevalence of HBsAg in HIV-infected patients might be higher than 6.4%.

In a previous questionnaire study of HIV–HCV co-infection, the prevalence of HCV infection among HIV-infected patients was 19.2%;[16] the prevalence of HBV infection (6.4%), is one-third of it. The lower positivity for HBsAg than for the anti-HCV antibody among those who contracted HIV through blood products accounts for this difference: almost all (96.9%) of the patients who contracted HIV through blood products were also anti-HCV antibody positive.[16] It should be noted that among the homosexual male patients who were HIV positive, 8.3% were HBsAg positive, which is twice as high as that of the anti-HCV antibody in these populations. A higher prevalence of HBV infection as a sexually transmitted infection than that of HCV[17] may explain the high prevalence of HBV infection in HIV-positive homosexual men. Similarly, a HBV prevalence of 3.4% in heterosexually transmitted HIV-positive patients is higher than that of the general Japanese population of the same age.[15]

Of the 377 patients who were HBsAg positive, 122 (32.4%) had elevated serum ALT levels at least once in the 1-year observation period. In this type of study using a questionnaire, it is difficult to obtain the details of patients' data, including age, body weight, and the degrees of liver injuries and fibrosis. If detailed items were included in the questionnaire, then the collection rate would be low. This time, to obtain a high collection rate, we asked whether the patients with HBsAg showed an elevated ALT level higher than 100 IU/L at least once during the 1-year observation period. We thereby do not have details on liver disease in HIV–HBV co-infected patients in the current study. Nonetheless, one-third of HIV–HBV co-infected patients have moderate liver injuries, either chronic hepatitis B or adverse effects of drugs, and are waiting for an aid for the amelioration of liver disease. A detailed analysis of the progression and activity of liver disease in HIV–HBV co-infected patients is expected.

The collection rate of the present questionnaire from the hospitals belonging to the HIV/AIDS Network was 55.6% (207 of 372). This was higher than that (47.8%) in the HIV–HCV co-infection questionnaire study carried out in 2003. The reason for this increase is not clear, but presumably the questionnaire conducted in 2003 has raised awareness among hospital staff regarding the relevance of hepatitis virus and HIV co-infection in clinical practice.

In the current study, both Japanese patients and those of other nationalities/ethnicities were included in the study. Although the ratio of newly diagnosed HIV-positive foreign people has been declining to approximately 10% in 2006, the one in total HIV positive still accounts for approximately 25% in Japan. Because the rates of the HBV carrier are different among countries, it is ideal to analyze the HBV prevalence separately according to the nationalities/ethnicities. However, in the current survey to the hospitals in HIV/AIDS Network of Japan, nationality/ethnicity was not itemized in order to make the questionnaire simple. If we would attempt to obtain such data under the approval of the ethical committee in each hospital, the response rate to questionnaire would be extremely lowered.

To establish measures that decrease the morbidity and mortality of HIV–HBV co-infected patients, it is essential to determine the current status of co-infection. In the present study, the number and transmission routes of HIV–HBV co-infected patients in Japan were determined for the first time, although detailed information on the severity and progression of liver disease in HIV–HBV co-infected patients has not been obtained yet. Undoubtedly, this will be the first step towards improving the prognosis and quality of life of Japanese patients co-infected with HIV and HBV.

ACKNOWLEDGMENTS

WE THANK MS. Ogawa for her assistance in the questionnaire inquiry. This work was supported in part by Health Sciences Research Grants from the Ministry of Health, Labor, and Welfare of Japan (Research on HIV/AIDS). We thank the hospitals in the HIV/AIDS Network of Japan for the responses to the questionnaire. The list of hospitals can be view at http://www.acc.go.jp/mLhw/mLhw_frame.htm.

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Hepatology Research 2007; **37**: 2–5 doi: 10.1111/j.1872-034X.2007.00011.x

Original Article

Prevalence of coinfection with human immunodeficiency virus and hepatitis C virus in Japan

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People with human immunodeficiency virus (HIV) infection are frequently infected with hepatitis C virus (HCV), because of the common transmission routes. Since the dissemination of hyperactive antiretrovirus therapy (HAART), the morbidity and mortality associated with HIV infection have declined. However, the reduction in mortality due to opportunistic infection has made HCV-associated liver diseases the leading cause of mortality in Western countries. A similar situation is assumed in Japan, but the status of coinfection with HIV and HCV is unclear. We conducted a nationwide survey to determine the prevalence of coinfection with HIV and HCV by distributing a questionnaire to the hospitals in the HIV/AIDS Network of Japan. Among 4877 patients reported to be HIV-positive, 935 (19.2%) were also positive for the anti-HCV antibody. Most (84.1%) of the patients coinfected with HIV and HCV were recipients of blood products. These data, for the first time, show the current status of coinfection with HIV and HCV in Japan. A detailed analysis of the progression and severity of liver diseases in the coinfected patients is expected.

Key words: coinfection, hepatitis C, HIV, liver disease

INTRODUCTION

HEPATITIS C VIRUS (HCV) infection and human immunodeficiency virus (HIV) infection are major public health problems worldwide. In the USA, the estimated prevalence of the anti-HCV antibody is 1.8%, with 2.7 million people having HCV-RNA detected in their blood, indicative of ongoing HCV infection.[1] The prevalence of HIV is <1%, and the virus is estimated to have infected approximately 800 000 people.[2] Because of the common transmission routes, that is, parenteral ones, many people with HIV infection are also infected with HCV.[3] Before the introduction of hyperactive antiretroviral treatment (HAART) in 1996, most people with HIV infection died of HIV-associated opportunistic infections such as *Pneumocystis carinii* (currently called *P. jiroveci*) pneumonia and cytomegaloviral infection. Since the dissemination of HAART, the morbidity and mortality associated with HIV infection have declined. However, the reduction in mortality due to opportunistic infection has made patients coinfected with HIV and HCV faced with the menace of progressive liver diseases due to HCV infection in the United States and Europe.[4,5]

Coinfection with HIV has been shown to increase the HCV load in HCV infection,[6] being a negative prognostic factor for clearance of HCV in anti-HCV therapy using interferon.[7,8] It also accelerates the development of cirrhosis and, eventually, hepatocellular carcinoma. Although still controversial, coinfection with HIV and HCV yields a more rapid progression to acquired immunodeficiency syndrome (AIDS) in some cases.[9,10] Importantly, coinfection with HIV and HCV will increase the morbidity and mortality of HIV-infected patients also in Japan, where the prevalence of HIV infection is increasing in a linear fashion, exceptionally among developed countries.[11] There are more than 10 000 HIV-positive people in Japan as of the end of 2004, according to the AIDS National Survey in Japan,[12] and approximately 1.8 million chronic HCV carriers, according to the estimation by the Ministry of Health, Labor and Welfare (MHLW) of Japan. However, unfortunately, the prevalence of coinfection with HIV and HCV in Japan has been unclarified to date. Therefore, we conducted a nationwide study by distributing an

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Received 7 August 2006; revision 22 August 2006; accepted 29 August 2006.

email-based questionnaire to the hospitals in the HIV/AIDS Network of Japan.

METHODS

IN THE QUESTIONNAIRE, the following information was obtained from hospitals regarding the number of patients who visited the hospitals at least once between January and December 2003: (1) the number of HIV-positive patients; (2) the number of anti-HCV-positive patients among (1); (3) the number of HCV-RNA-positive patients among (2); (4) the number of HIV-positive patients who contracted HIV from blood products; (5) the number of anti-HCV-positive patients among (4); (6) the number of HCV-RNA-positive patients among (5); (7) the number of HIV-positive patients among men who have sex with men (MSM); (8) the number of anti-HCV-positive patients among (7); (9) the number of HCV-RNA-positive patients among (8); (10) the number of HIV-positive patients who contracted HIV through intravenous drug use; (11) the number of anti-HCV-positive patients among (10); (12) the number of HCV-RNA-positive patients among (11); (13) the number of HIV-positive patients whose transmission routes were classified as 'others'; (14) the number of anti-HCV-positive patients among (13); and (15) the number of HCV-RNA-positive patients among (14).

The questionnaire was sent to the 366 hospitals in the HIV/AIDS Network of Japan by email. When emails were returned with a failure of delivery, the questionnaire was forwarded by post. Answers were mostly returned by email, and in some cases by fax. The list of the hospitals in the HIV/AIDS Network of Japan can be browsed at: http://www.acc.go.jp/mLhw/mLhw_frame.htm.

RESULTS

THE QUESTIONNAIRE WAS sent to all 366 hospitals that were on the list of hospitals in the HIV/AIDS Network of Japan in January 2004. One hundred and seventy-six hospitals (48.1%) responded within the indicated period. A collection rate of 47.8% may appear rather low, particularly considering the number of reported HIV-positive people, 10 000, in 2004 according to the statistics of the MHLW of Japan.[12] However, not all the HIV-positive cases are visiting hospitals, and answers to the questionnaire were obtained from most of the major hospitals in the HIV/AIDS Network in big cities around Japan. These factors suggest that not all but a majority of HIV-positive patients in Japan were enrolled in the study.

Table 1 Number of hospitals categorized by the number of patients infected with HIV and those coinfected with HIV and HCV

No. of HIV(+)/HCV(+)	No. of HIV(+)				
	0	1–19	20–49	50+	Total
0	43	52	5	1	101
1–9	0	45	9	3	57
10+	0	2	4	12	18
Total	43	99	18	16	176

There were one or more HIV-positive patients in 133 of 176 (75.6%) hospitals; there were no HIV-positive patients in the remaining 43 hospitals (Table 1). Eighteen of 176 (10.2%) hospitals had 20–49 HIV-positive patients, and 16 (9.1%) hospitals had 50 or more HIV-positive patients. On the other hand, there were one or more patients who were coinfected with HIV and HCV in 75 (42.6%) of 176 hospitals, and there were 10 or more HIV/HCV coinfected patients in 18 (10.2%) hospitals. HIV/HCV coinfected patients were concentrated in specific hospitals in big cities around Japan. In particular, in the Kanto area, HIV/HCV coinfected patients were concentrated in the HIV/AIDS Network hospitals in the Tokyo city area (Fig. 1). Of the 16 hospitals with 50 or more HIV-positive patients and of the 18 hospitals with 10 or more HIV/HCV coinfected patients, 12 were the same hospitals (Table 1). Hospitals with 10 or more HIV/HCV coinfected patients, but with less than 50 HIV-positive patients had the characteristic that most HIV-positive patients contracted HIV from blood products.

In total, 4877 patients were reported to be HIV-positive. Among these, 935 (19.2%) were positive for anti-HCV (Table 2). Of these 935 patients, 780 were HCV-RNA-positive, although it should be noted that not all the patients underwent HCV-RNA testing.

HCV prevalence when fractionated by routes of transmission was as follows. Among 811 HIV-positive patients who contracted HIV from blood products such as unheated concentrated coagulation factors, 786 (96.9%) were anti-HCV-antibody-positive. Of 20 intravenous drug users, nine (45.0%) were anti-HCV-antibody-positive. Among 2730 HIV-positive patients who were MSM (men who have sex with men), 114 (4.2%) were anti-HCV positive. In the remaining 1316 HIV-positive patients whose routes of HIV transmission

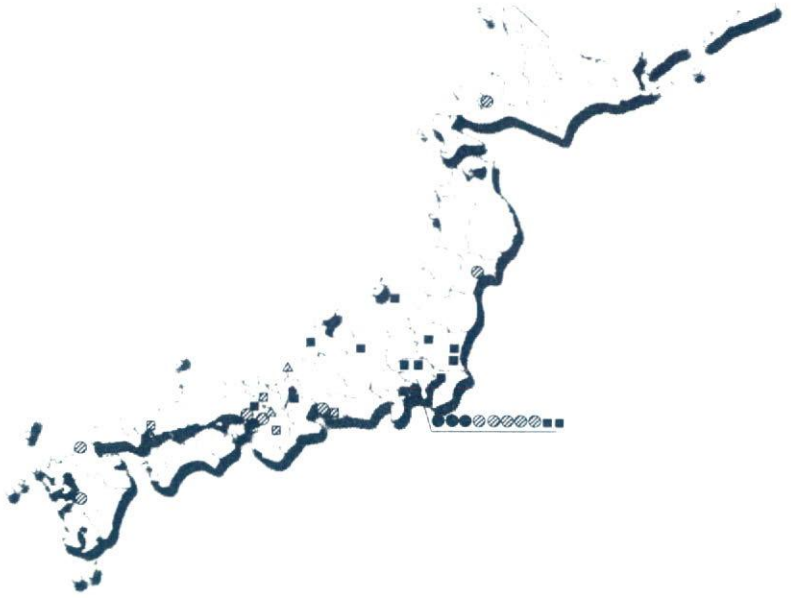

Figure 1 Nationwide distribution of hospitals in the HIV/AIDS Network of Japan that a number of HIV-positive or HIV/HCV coinfected patients are visiting regularly. Note that in the Kanto area, HIV/HCV coinfected patients were concentrated in the HIV/AIDS Network hospitals in the Tokyo city area. (△) hospitals with 1–19 HIV-positive patients; (□) hospitals with 20–49 HIV-positive patients; (○) hospitals with 50+ HIV-positive patients. Hatched figures: hospitals with 10 or more HIV/HCV coinfected patients. Closed figures: hospitals with less than 10 HIV/HCV coinfected patients. For easier visual comprehension, hospitals with 19 or less HIV-positive patients and 9 or less HIV/HCV coinfected patients are omitted from the figure.

were classified as "others", most of whom contracted HIV heterosexually, 26 (2.0%) were anti-HCV-antibody-positive. On the other hand, in HIV/HCV coinfected patients, 786 (84.1%) of 935 patients were recipients of blood products. Thus, the majority of HIV/HCV coinfected patients in Japan are those who contracted HIV, and most likely also HCV, from blood products.

DISCUSSION

ACCORDING TO THE statistics of the MHLW of Japan, the number of reported HIV-positive people was just over 10 000 in 2004.[12] The total number of HIV-positive patients in the current study is approximately half of that. By a simple calculation, there would be about 1900 HIV/HCV coinfected patients in Japan. However, because HIV-positive patients who contracted HIV from blood products are almost all registered in Japan and most of them should have been enrolled in this survey, the number of HIV/HCV coinfected patients is likely smaller than 1900. It is regrettable that not all the patients underwent HCV-RNA testing, but it is unavoidable in this type of questionnaire-based study. In some cases, the existence of a positive anti-HCV antibody indicates a memory of a remote HCV infection.

Almost all of the patients who contracted HIV through blood products were also anti-HCV-antibody-positive, suggesting that both viruses were transmitted through the same route. In MSM patients who were HIV-positive, approximately 4% were anti-HCV-antibody-positive, which is about threefold higher than the prevalence of HCV in Japan.[13] In people aging from 40 to 50 years old in the general Japanese population, whose ages are similar to those of the MSM patients in the current study, the prevalence of HCV is less than 0.5%.[13] Therefore, an HCV prevalence of 4% in MSM

Table 2 Prevalence of HCV infection in HIV-positive patients

Routes of transmission	No. of patients	Anti-HCV-positive	HCV-RNA-positive†
Blood products	811	786 (96.9%)	667
MSM‡	2730	114 (4.2%)	98
Drug addicts	20	9 (45.0%)	8
Others (heterosexual etc.)	1316	26 (2.0%)	7
Total	4877	935 (19.2%)	780

†Not all patients were subjected to HCV-RNA test. ‡MSM, men who have sex with men.

HIV-positive patients is quite high, suggesting the same route of the transmission of HIV and HCV, and a more intensive exposure to HCV or more susceptibility to HCV in these HIV-positive patients. Similarly, an HCV prevalence of 1.4% in heterosexually transmitted HIV-positive patients is higher than that of the general Japanese population of the same age.

To establish measures that decrease the morbidity and mortality of HIV/HCV coinfected patients, it is essential to recognize the current status of the coinfection. In the present study, the number and transmission routes of HIV/HCV coinfected patients in Japan were first described, although detailed information on the progression of HCV-associated liver diseases in HIV/HCV coinfected patients has not yet been obtained. Undoubtedly, this will be the first step for improving the prognosis and quality of life of patients coinfected with HIV and HCV in Japan. A detailed analysis of the progression and severity of HCV-associated liver diseases is expected.

ACKNOWLEDGMENTS

WE THANK MS. Ogawa for her assistance in questionnaire inquiry. This work was supported in part by Health Sciences Research Grants from the Ministry of Health, Labor and Welfare of Japan. We thank the Hospitals in HIV/AIDS Network of Japan for the responses to the questionnaire, the list of which can be browsed at http://www.acc.go.jp/mLhw/mLhw_frame.htm.

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HIV 診療支援ネットワークを活用した診療連携の利活用に関する研究

（H17-エイズ-001）

H17 年度　主任研究者　秋山　昌範

添付資料　　HIV 診療支援システム現状調査

注：本資料は、平成 17 年 4 月 1 日～平成 18 年 3 月 31 日の HIV 診療支援システムの調査状況を H17 年度に報告書にまとめたものの転載です。

目次

システム性能指標

データ収集方法

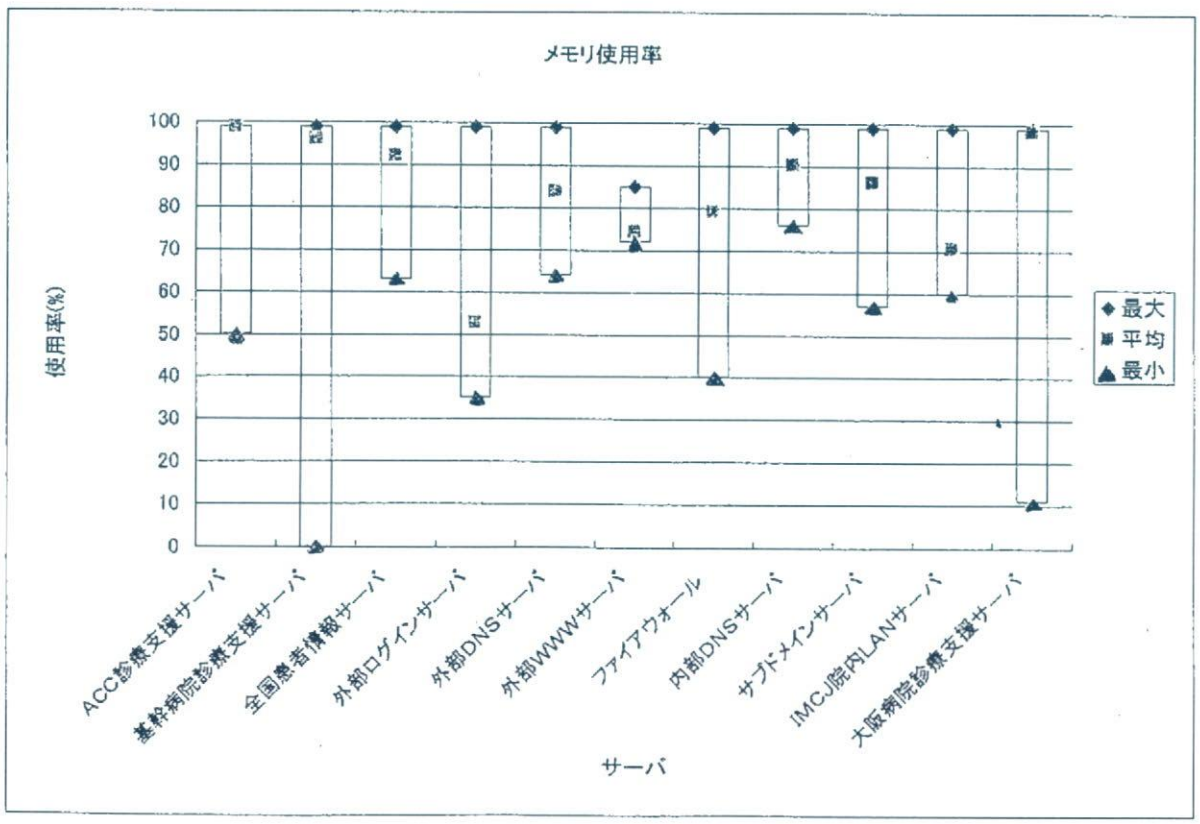
- 各性能指標値は、1時間おきにデータを収集し、1日単位に最大・最小・平均値を求めたものです。
- メモリ使用率は、vmstatコマンドを基にフリーメモリ量を計算しています。
- ページング使用率は、lspsコマンドを基にページングデバイス使用率を計算しています。
- CPU使用率は、vmstatコマンドを基にuserモードの使用率を計算しています。

サマリ

1年間のデータを集計しています。

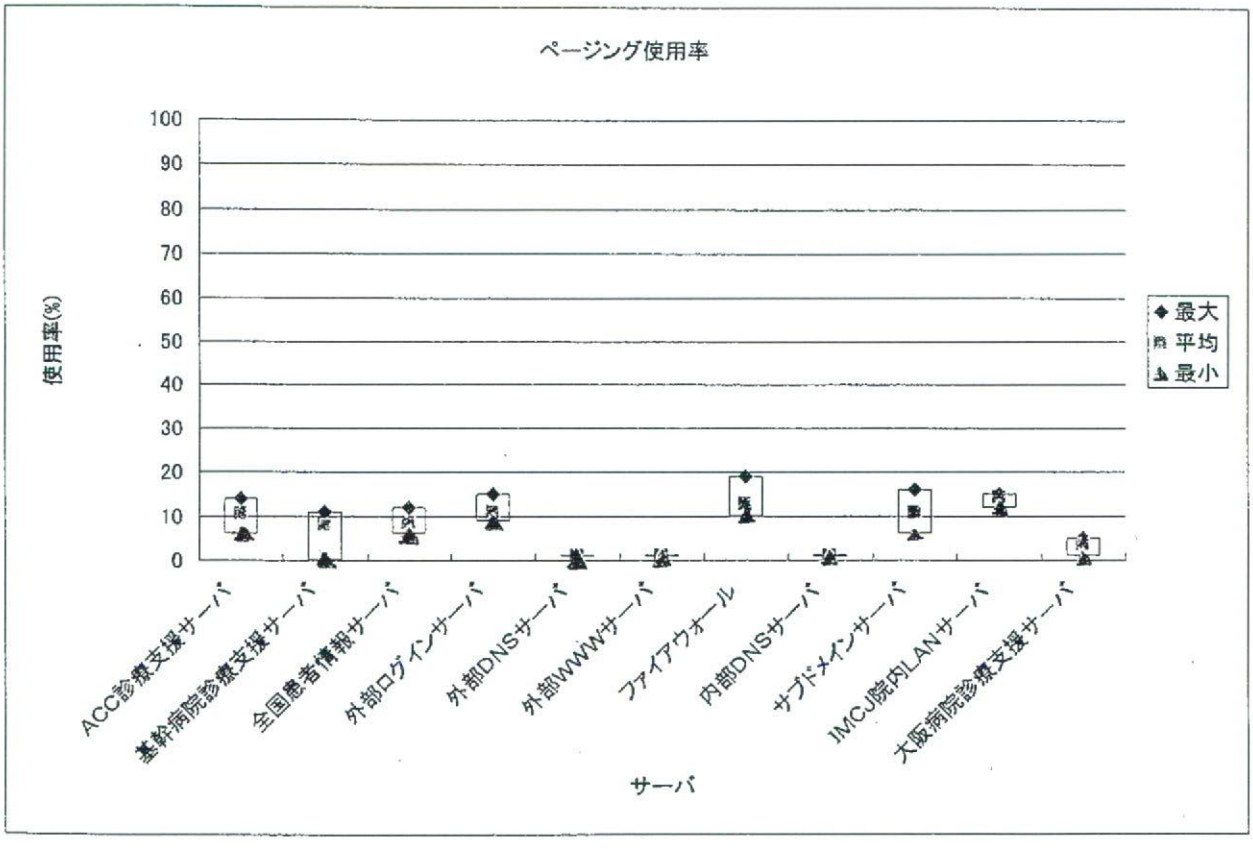
メモリ使用率

メモリ使用率(%)	最大	平均	最小
ACC診療支援サーバ	99	98.78	50
基幹病院診療支援サーバ	99	96.11	0
全国患者情報サーバ	99	92.24	63
外部ログインサーバ	99	52.93	35
外部DNSサーバ	99	83.95	64
外部WWWサーバ	85	74.46	72
ファイアウォール	99	79.37	40
内部DNSサーバ	99	90.34	76
サブドメインサーバ	99	86.25	57
IMCJ院内LANサーバ	99	70.75	60
大阪病院診療支援サーバ	99	98.40	11



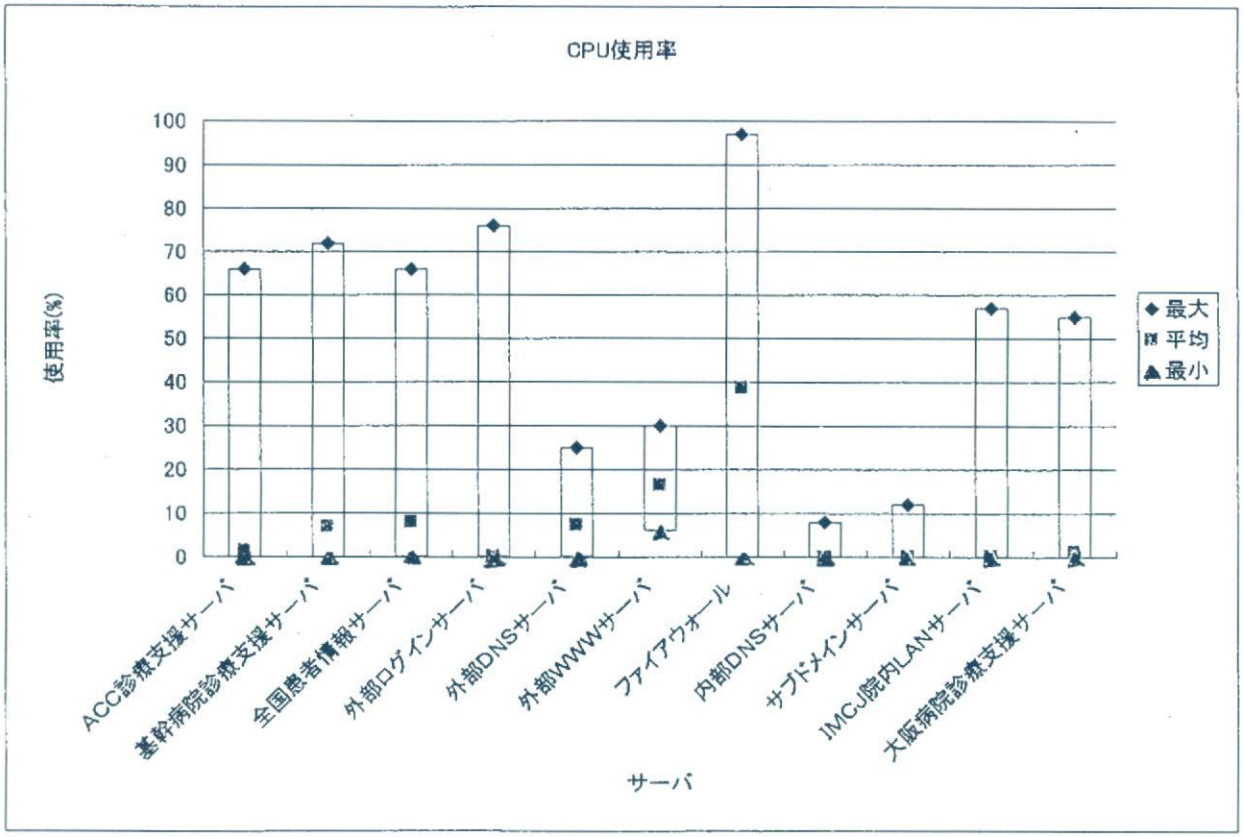
ページング使用率

ページング使用率(%)	最大	平均	最小
ACC診療支援サーバ	14	10.67	6
基幹病院診療支援サーバ	11	8.03	0
全国患者情報サーバ	12	8.62	6
外部ログインサーバ	15	10.98	9
外部DNSサーバ	1	1.00	1
外部WWWサーバ	1	1.00	1
ファイアウォール	19	12.79	10
内部DNSサーバ	1	1.00	1
サブドメインサーバ	16	10.81	6
IMCJ院内LANサーバ	15	14.30	12
大阪病院診療支援サーバ	5	3.65	1



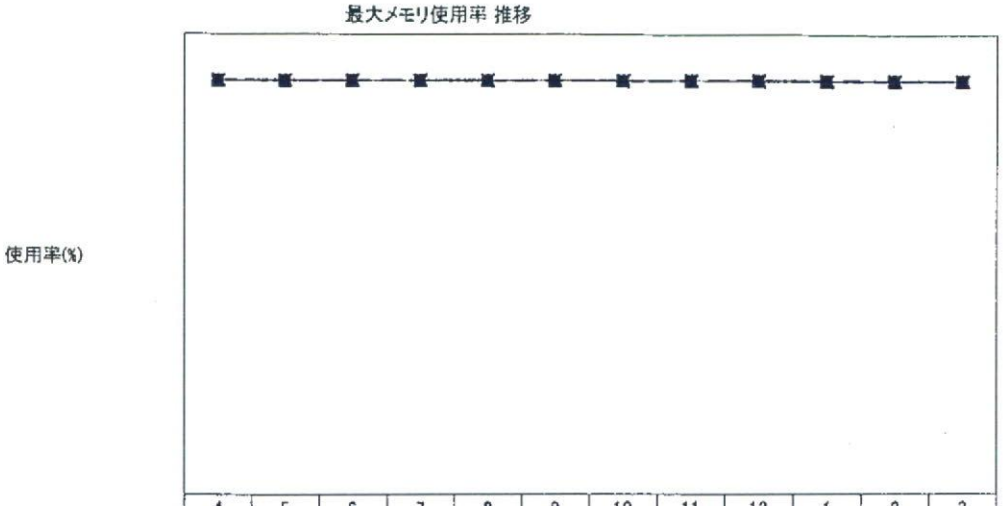
CPU使用率

CPU使用率(%)	最大	平均	最小
ACC診療支援サーバ	66	1.47	0
基幹病院診療支援サーバ	72	6.91	0
全国患者情報サーバ	66	7.93	0
外部ログインサーバ	76	0.11	0
外部DNSサーバ	25	7.46	0
外部WWWサーバ	30	16.58	6
ファイアウォール	97	38.67	0
内部DNSサーバ	8	0.00	0
サブドメインサーバ	12	0.18	0
IMCJ院内LANサーバ	57	0.15	0
大阪病院診療支援サーバ	55	1.20	0



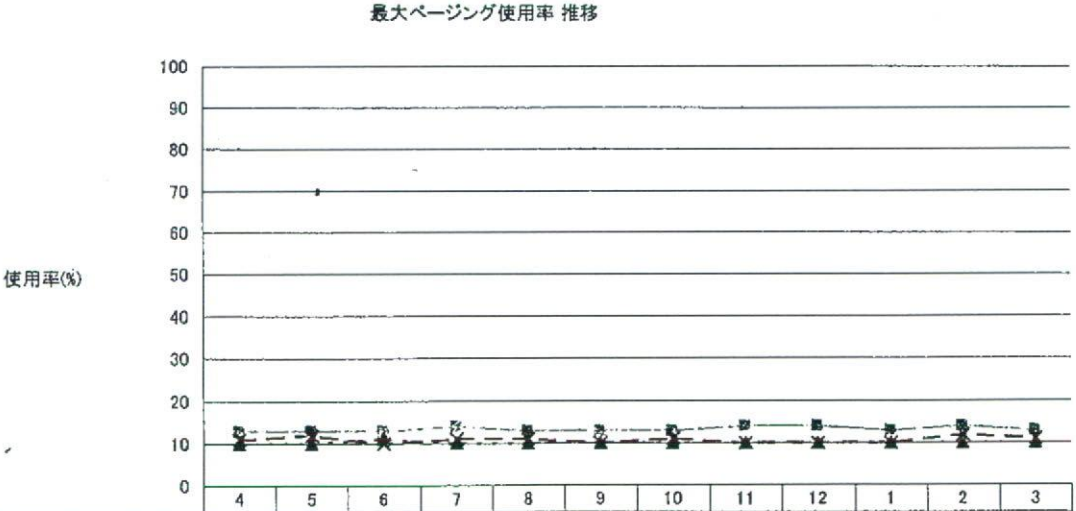
アプリケーション系システム性能指標

メモリ使用率



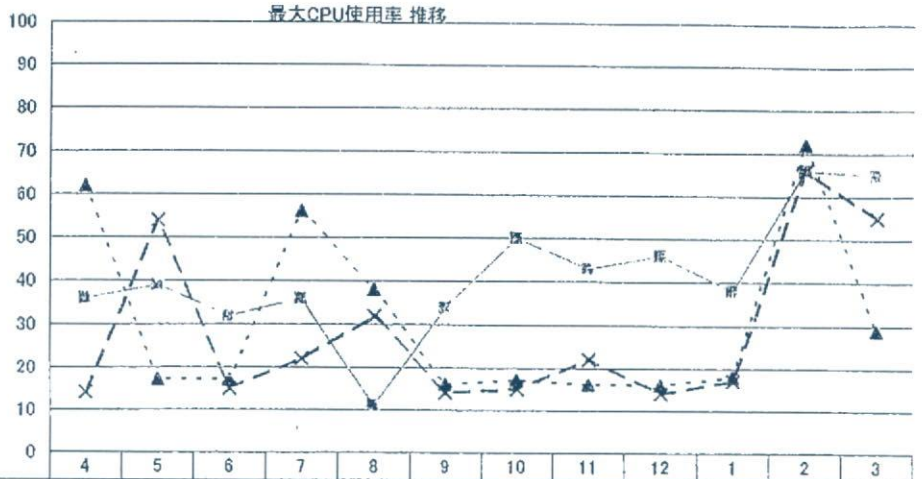
	4	5	6	7	8	9	10	11	12	1	2	3
ACC診療支援サーバ	99	99	99	99	99	99	99	99	99	99	99	99
基幹病院診療支援サーバ	99	99	99	99	99	99	99	99	99	99	99	99
全国患者情報サーバ	99	99	99	99	99	99	99	99	99	99	99	99

ページング使用率



	4	5	6	7	8	9	10	11	12	1	2	3
ACC診療支援サーバ	13	13	13	14	13	13	13	14	14	13	14	13
基幹病院診療支援サーバ	10	10	11	10	10	10	10	10	10	10	10	10
全国患者情報サーバ	11	12	10	11	11	10	11	10	10	10	12	11

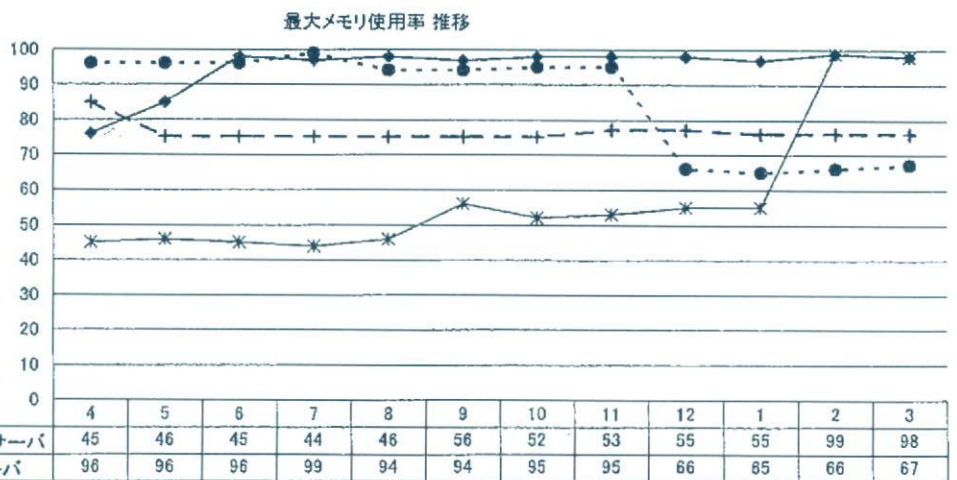
CPU使用率



	4	5	6	7	8	9	10	11	12	1	2	3
ACC診療支援サーバ	36	39	32	36	11	34	50	43	46	38	66	65
基幹病院診療支援サーバ	62	17	17	56	38	16	17	16	16	18	72	29
全国患者情報サーバ	14	54	15	22	32	14	15	22	14	17	66	55

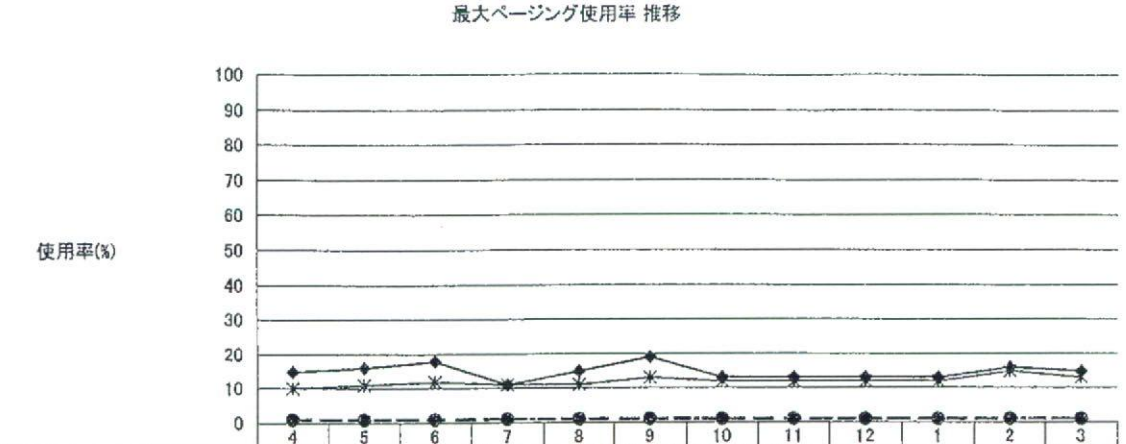
基板系[外部]システム性能指標

メモリ使用率



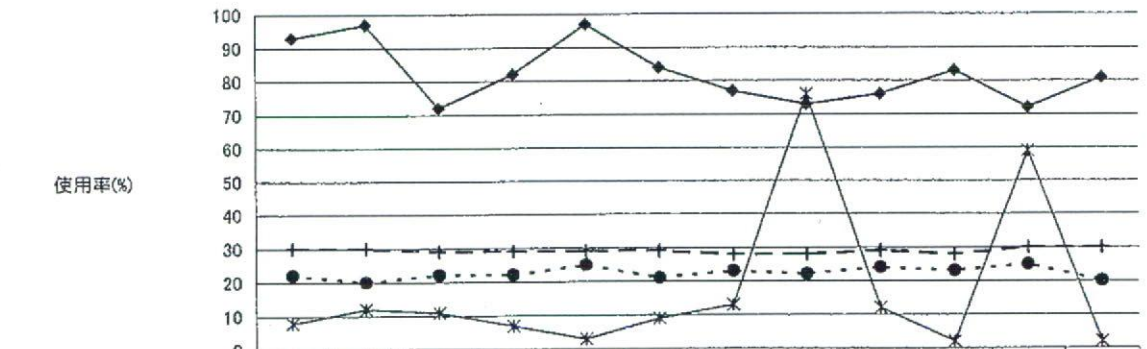
	4	5	6	7	8	9	10	11	12	1	2	3
外部ログインサーバ	45	46	45	44	46	56	52	53	55	55	99	98
外部DNSサーバ	96	96	96	99	94	94	95	95	66	65	66	67
外部WWWサーバ	85	75	75	75	75	75	75	77	77	76	76	76
ファイアウォール	76	85	98	97	98	97	98	98	98	97	99	98

ページング使用率



	4	5	6	7	8	9	10	11	12	1	2	3
外部ログインサーバ	10	11	12	11	11	13	12	12	12	12	15	13
外部DNSサーバ	1	1	1	1	1	1	1	1	1	1	1	1
外部WWWサーバ	1	1	1	1	1	1	1	1	1	1	1	1
ファイアウォール	15	16	18	11	15	19	13	13	13	13	16	15

CPU使用率



	4	5	6	7	8	9	10	11	12	1	2	3
外部ログインサーバ	8	12	11	7	3	9	13	76	12	2	59	2
外部DNSサーバ	22	20	22	22	25	21	23	22	24	23	25	20
外部WWWサーバ	30	30	29	29	29	29	28	28	29	28	30	30
ファイアウォール	93	97	72	82	97	84	77	73	76	83	72	81