antigen-specific T-cell immunity, is likely to be substantially shaped by early events in the innate response to the pathogen (Chang and others 2008). Considering that IL-12 is a key cytokine in the induction of CD4 T-cell activation, whereas IL-10 has complex inhibitory effects (Yee and others 2001), HCV-induced modulation of these cytokines may have special importance in altered HCV-specific T-cell responses in chronic HCV infection. IL-12 and IL-15 are biomarkers for the innate immune response.

The level of CXCL-8 was significantly increased. Because CXCL-8, the production of which is stimulated by HCV NS5A, is able to directly inhibit the antiviral activity of IFN-α, higher levels of CXCL-8 in nonresponders may contribute in part to the poor response to IFN-α therapy (Polyak and others 2001). The level of CCL-11 was also significantly higher. CXCL-10, like other β-chemokines, has been shown to be a chemoattractant for monocytes and activated T cells. CCL-4-mediated T-cell infiltration is essential for activated T cells and for the delivery of IFN-γ to mediate downstream protective responses against HCV infection in the liver (Narumi and others 1997). CCL-4 was upregulated in acute infection cases at the time of viral clearance, but not in those patients who failed to eradicate the virus (Bigger and others 2004), and HCV-infected individuals have a diminished response to CCL-4 in the liver (Lichterfeld and others 2002). CCL-2 is one of the most significant chemokines in chronic inflammatory diseases controlled by mononuclear leukocytes. Target cells include monocytes, hematopoietic precursors, mast cell, T lymphocytes, NK cells, and DCs.

These results, especially the significantly lower levels of IL-12 and the significantly higher levels of CXCL-8 in all CHC patients compared to the controls at baseline, suggested the impairment of innate immunity in all CHC patients compared to the controls.

Serial values of serum cytokines and chemokines during the NCT

At the end of CPIT, in all CHC patients, the levels of CCL-4 decreased significantly ($P < 0.05$), the levels of IFN-γ, TNF-α, IL-1α, IL-1β, IL-2, IL-4, GM-CSF, and G-CSF decreased, and the levels of IL-9, IL-10, IL-13, IL-15, CCL-2, PDGF, and VEGF increased from baseline. In EAVR, the levels of CCL-4 decreased significantly ($P < 0.05$) from baseline but only to a lesser extent in LAVR. The levels of CCXL-8 decreased in EAVR but increased significantly ($P < 0.05$) in LAVR. This result suggested the restoration of antiviral activity of type I IFN inhibited by CXCL-8 in EAVR but not in LAVR. IL-10 levels increased in LAVR but were not changed in EAVR at the end of CPIT. Increased levels of IL-15 at the end of CPIT suggested that initial viral clearance, induced by CPIT before the beginning of RBV plus PEG-IFN-α2b therapy, improved the innate immune response to HCV involving Tregs-mediated immune response impairment (Fu and others 2007). The levels of CXCL-10, CCL-3, and PDGF decreased in EAVR but increased in LAVR at the end of CPIT. These results suggested that CPIT improved the innate immune response; however, there was insufficient improvement of adaptive immune response in CHC during NCT (Figures 2-4).

At the end of NCT, in CHC patients the levels of CCL-4 decreased significantly ($P < 0.05$) and the levels of IFN-γ, TNF-α, IL-1α, IL-1β, IL-2, IL-4 ($P < 0.1$), IL-6, IL-9, IL-15, CXCL-8, CXCL-10 ($P < 0.1$), CCL-3, CCL-11, PDGF, GM-CSF, and GCSF decreased from baseline. In EAVR, the levels of IFN-γ, IL-1α, CCL-4, and CXCL-8 decreased significantly ($P < 0.05$) and the levels of CXCL-10 decreased ($P < 0.1$) from baseline. In LAVR, the levels of IFN-γ, IL-1α, and CCL-4 decreased and CXCL-8 increased. The levels of IL-9, GCSF ($P < 0.1$), and CXCL-10 ($P < 0.1$) decreased in EAVR but not in LAVR. The levels of IL-6, IL-12, IL-15, and CCL-3 ($P < 0.1$) decreased in LAVR but not in EAVR. CPIT induced the upregulation of IL-15, but RBV/PEGIFN-α2b did not. IL-10 and VEGF increased in LAVR but unchanged in EAVR.

Four weeks after the end of NCT, in all CHC patients, the levels of IL-12 and VEGF increased significantly ($P < 0.05$), and IL-10 ($P < 0.1$) and CCL-2 (MCP-1) increased from baseline. The levels of IFN-γ, TNF-α, IL-1α, IL-1β, IL-2, IL-4, IL-6, CXCL-8 (IL-8), CXCL-10 (IP-10) ($P < 0.1$), CCL-4 (MIP-1β) ($P < 0.1$), CCL-11, GM-CSF,, and G-CSF decreased from baseline. The levels of IL-12 and VEGF increased significantly ($P < 0.05$) in EAVR but did so to a lesser extent in LAVR. The levels of IL-15 and CCL-2 increased in EAVR but decreased in LAVR. The levels of IL-13 increased ($P < 0.1$) in LAVR but did so to a lesser extent in EAVR. The levels of CXCL-10 ($P < 0.1$) decreased in EAVR but did so to a lesser extent in LAVR. CXCL-8 and CCL-3 levels were unchanged in EAVR but decreased in LAVR.

These results suggested that early virological clearance by CPIT before beginning RBV/PEG-IFN-α treatment induced the restoration of innate immune responses and lead to antiviral responses and persistent virological clearance for more than 48 weeks with the subsequent RBV/PEG-IFN-α therapy induced restoration of innate immune responses linked to adaptive immune responses and resulting in SVR and SBR.

Correlation of serum cytokine and chemokine to therapeutic responses

Figures 3–4 show that the IL-15 level increased in EAVR and LAVR at the end of CPIT and 4 weeks after the end of NCT in EAVR but not in LAVR. The level of CXCL-8 decreased significantly in EAVR but not in LAVR during NCT. After the end of NCT, in EAVR but not in LAVR, the IL-12 level increased significantly and the CXCL-8 level decreased significantly. Interestingly, CCL-8 increased in LAVR at the end of CPIT and NCT.

There appear to be innate immune responses that control the levels of virus and lead to significant decreases in HCVRNA titer with SVR. The timing of these responses is not the same for EAVR and LAVR. There is a distinct shift at the point at which viral replication began to decrease in the individual HCVRNA titers. The delay in the induction of the innate immune response that caused this decrease results in continued viral replication, which may account for the higher peak HCVRNA titers seen in the non-SVR group. This delay may lead to immune escape or exhaustion of the induced response as a result of high numbers of infected cells (Bigger and others 2004).

Adverse effects

NCT was well tolerated, but general fatigue, alopecia, and depression were more frequent during IFN-α treatment than during nIFN-β treatment. On the other hand, transient proteinuria, thrombocytopenia, and leucopenia were more frequent during nIFN-β treatment than during IFN-α

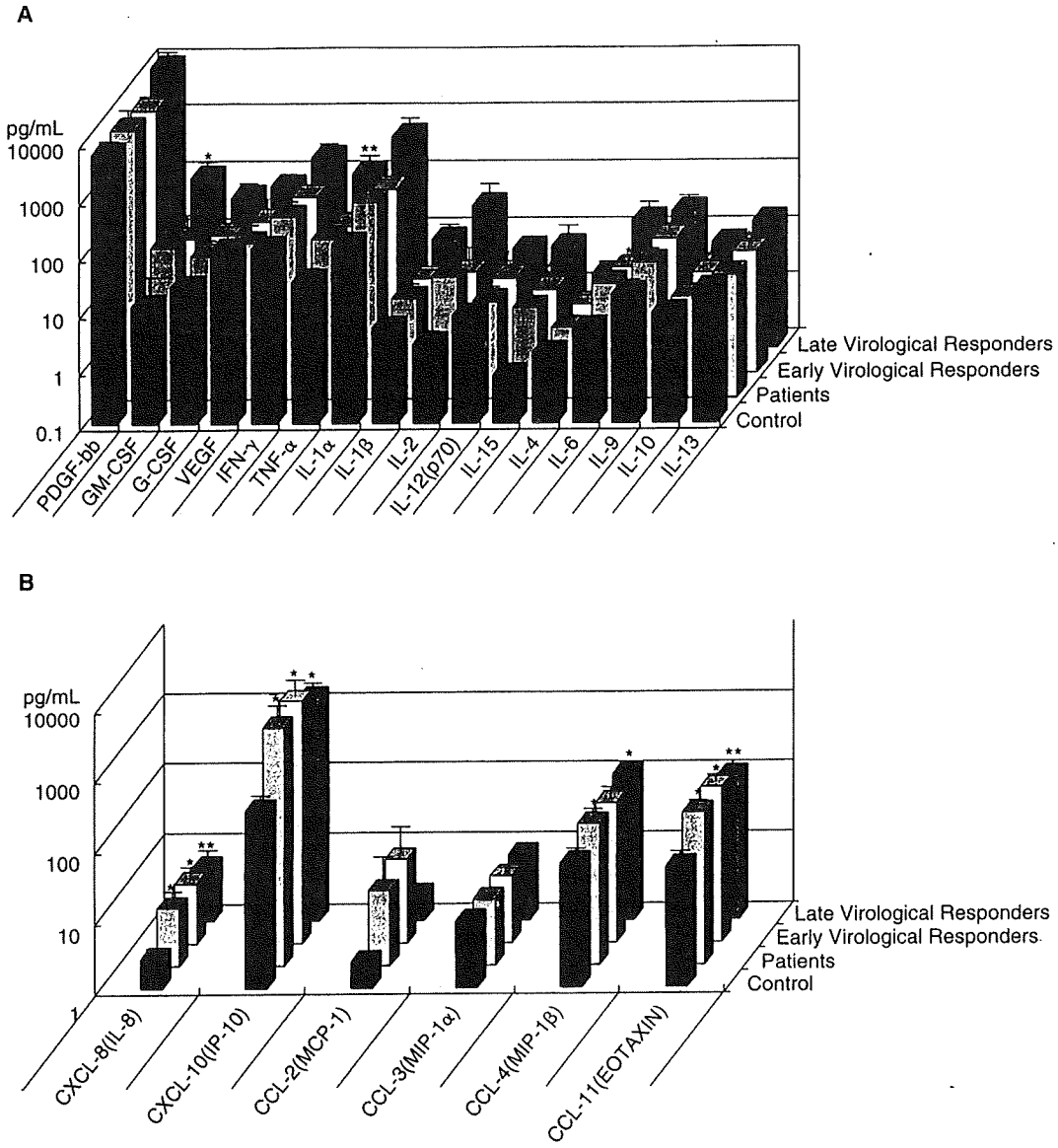

FIG. 1. Levels of serum cytokines (A) and chemokines (B) at baseline in chronic hepatitis C patients with high viral load, genotype 1b (serotype I), and wild or intermediate types of ISDR. Significant difference: $^{*}P < 0.05$, $^{**}P < 0.1$. Abbreviation: ISDR, interferon sensitivity determining region.

treatment. Hemoglobin levels decreased during RBV plus PEG-IFN-α2b treatment (Table 2). It is known that in patients who adhere to a treatment, response much better than those who do not (Sharma and others 2007). In this study, none of the patients dropped out from the protocol. There was no discontinuation of NCT, but reduction in the dose of RBV and/or IFN was applied as necessary.

Discussion

Because the resolution of an HCV infection may also involve the innate immune system, including DCs and NK cells, HCV-specific immune responses are vigorous in patients who are spontaneously cleared of HCV during an acute infection and weak in those who develop a persistent infection, suggesting primary failure and secondary down-regulation or exhaustion of the HCV-specific immune response (Urbani and others 2002; Khakoo and others 2004; Rahman and others 2004). The results of this study suggested that differences between the SVR and non-SVR group were (1) the timing of the host immune response that controls viral replication occurred approximately 4–12 weeks later in the non-SVR group; and (2) a greater association of increased IFN-γ, TNF-α, IL-12 and IL-15, and decreased CXCL-8 levels with HCV viral clearance.

This might imply that reducing viral replication below a certain threshold could allow the natural immune response to gradually eliminate infected cells (Pawlotsky 2004). This hypothesis is supported by data from lymphocytic choriomeningitis and simian immunodeficiency virus models,

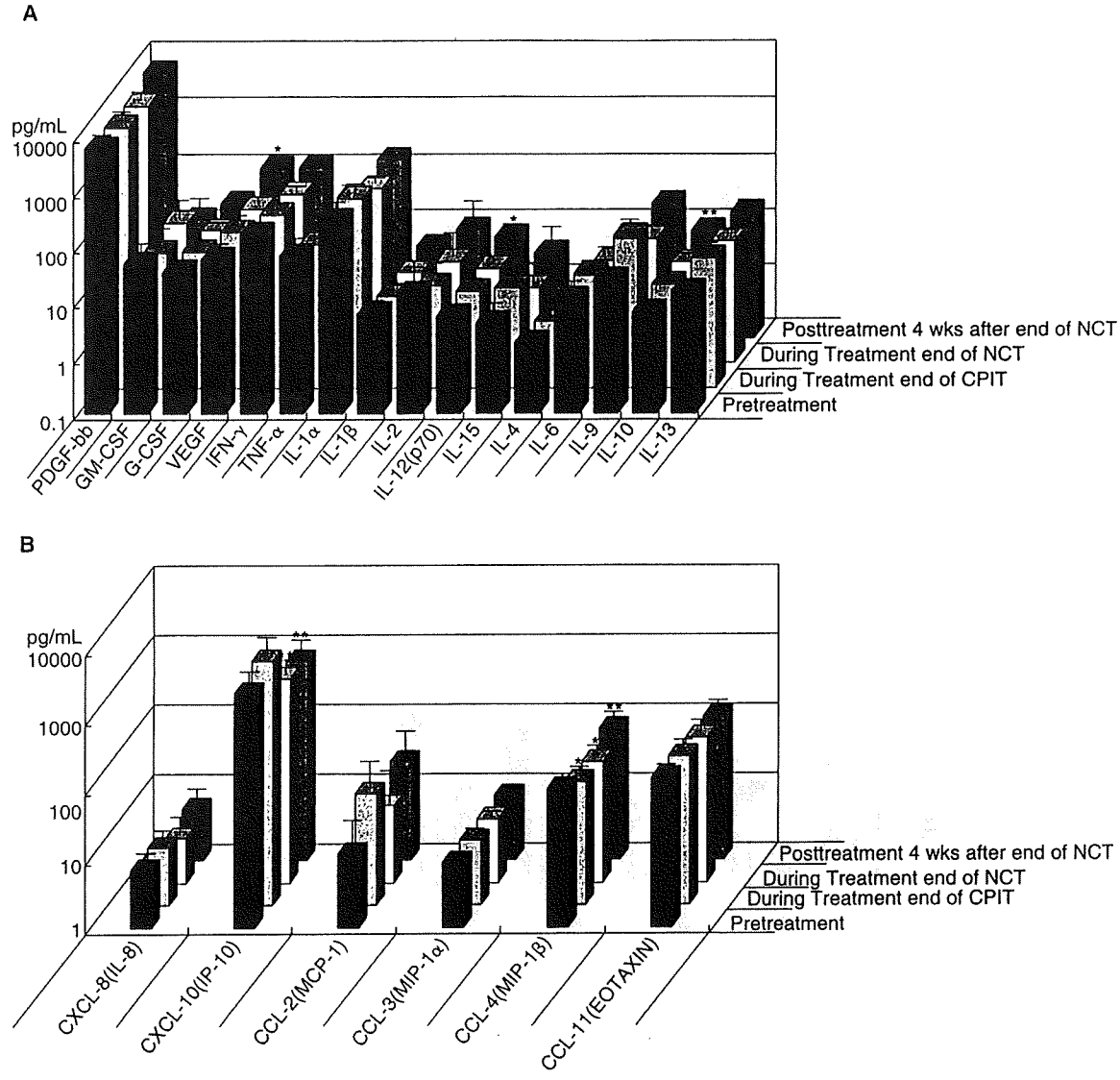

FIG. 2. Effect of RBV plus PEG-IFN-α2b using an "induction" approach with CPIT (NCT) on serum cytokines (A) and chemokines (B) in chronic hepatitis C patients with high viral load, genotype 1b (serotype I), and wild or intermediate type of ISDR (all patients). Significant difference: $^{*}P < 0.05$, $^{**}P < 0.1$. Abbreviations: RBV, ribavirin; PEG-IFN, pegylated interferon; CPIT, cyclic and periodic interferon treatment; NCT, novel combination treatment.

in which the early control of viral replication facilitates the development of virus-specific proliferative T-cell responses (Accapezzato and others 2004).

The reduction of HBV burden by lamivudine improves HBV-specific CD4 as well as CD8 T-cell responses (Boni and others 2001). The strategy of using an antiviral such as lamivudine initially to decrease the HBVDNA level before adding an immunomodulatory agent leads to improved SVR when compared with using the immunomodulator from the start, and is a novel approach for improving the efficacy of the treatment of chronic hepatitis B (Sarin and others 2007). Interaction between HCV proteins and components of the IFN regulatory pathways suggest that the virus has the capacity to disrupt this aspect of the immune response (Major and others 2004). Such findings have led to the suggestion that early antiviral therapy may prevent the downregulation or exhaustion of HCV-specific responses (Rahman and others 2004). Specifically, early antiviral therapy may decrease the number of quasispecies and prevent the emergence of HCV mutants that may escape or antagonize T-cell responses.

During IFN-α-based therapy, successful responses are associated with lasting and Th1-type CD4 T-cell responses (Rico and others 2002). The high viral production rate clarifies why HCV appears as a quasispecies as diverse as HIV and implies that mutations, which make the virus fitter during treatment, could be produced rapidly. Indeed, it was found that the failure of IFN treatment is associated with extensive quasispecies diversity and a high viral load.

The production of endogenous IFN-β, which plays crucial roles in innate immunity, is inhibited by the decreased

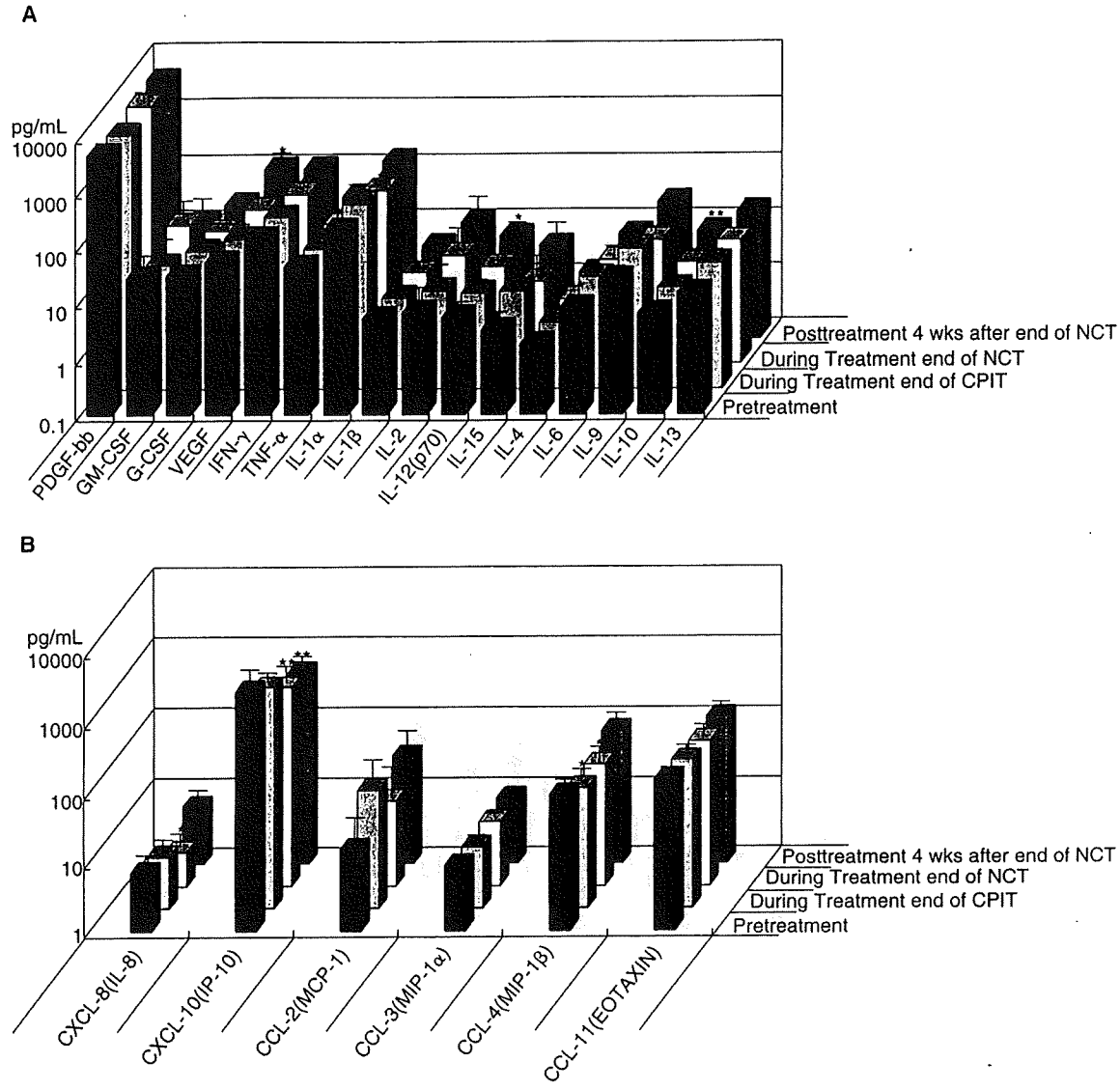

FIG. 3. Effect of RBV plus PEG-IFN-α2b using an "induction" approach with CPIT (NCT) on serum cytokines (A) and chemokines (B) in chronic hepatitis C patients with high viral load, genotype 1b (serotype I),and wild or intermediate type of ISDR (early virological responders). Significant difference: $^{*}P < 0.05$, $^{**}P < 0.1$. Abbreviations: RBV, ribavirin; PEG-IFN, pegylated interferon; CPIT, cyclic and periodic interferon treatment; NCT, novel combination treatment.

frequency of mDC and by the regulation of IRF-3 by HCV serine protease (Taniguchi and others 2001). Exogenous IFN-β gives a more rapid increase in the concentration of IFN in the blood and liver compared with exogenous IFN-α and can achieve early and rapid viral clearance. Therefore, IT with nIFN-β that does not induce virological breakthrough was thought to be optimal. However, IT with nIFN-β for a long period of time resulted in reduction of the levels of the IFN receptor, 2′-5′-OAS, and the activity of NK cells and AEs. To avoid this, switching to MT with IFN-α was considered to be necessary. However, MT with IFN-α for a long period of time led to virological breakthrough. To prevent virological breakthrough, re-IT with nIFN-β was thought to be necessary. CPIT consisting of repeated IT with nIFN-β followed by MT with IFN-α was conducted. In a preceding study (Kishida and others 2003), it was shown that (1) in difficult-to-treat CHC patients, CPIT enhanced the persistent increase in 2′-5′-OAS and also inhibited the emergence of IFN-resistant quasispecies, decreased the number of clones and bases in HVR1, and inhibited changes from the intermittent type to mutant type in NS5A; (2) MT with IFN-α without virological breakthrough showed that the reduction with no virus detection of serum HCV RNA was the greatest with a 2-week cycle; and (3) to achieve steady-state viral clearance, one cycle of CPIT comprised IT with nIFN-β daily for 2 weeks followed by MT with IFN-α three times weekly for 2 weeks. In a previous study (Kishida and others 2004), it was shown that CPIT for 24 weeks achieved cEVR (7/7, 100%), persistent viral clearance without viral breakthrough, and ETVR (7/7, 100%), SVR (2/7, 28.6%), and SBR (5/7, 71.4%)

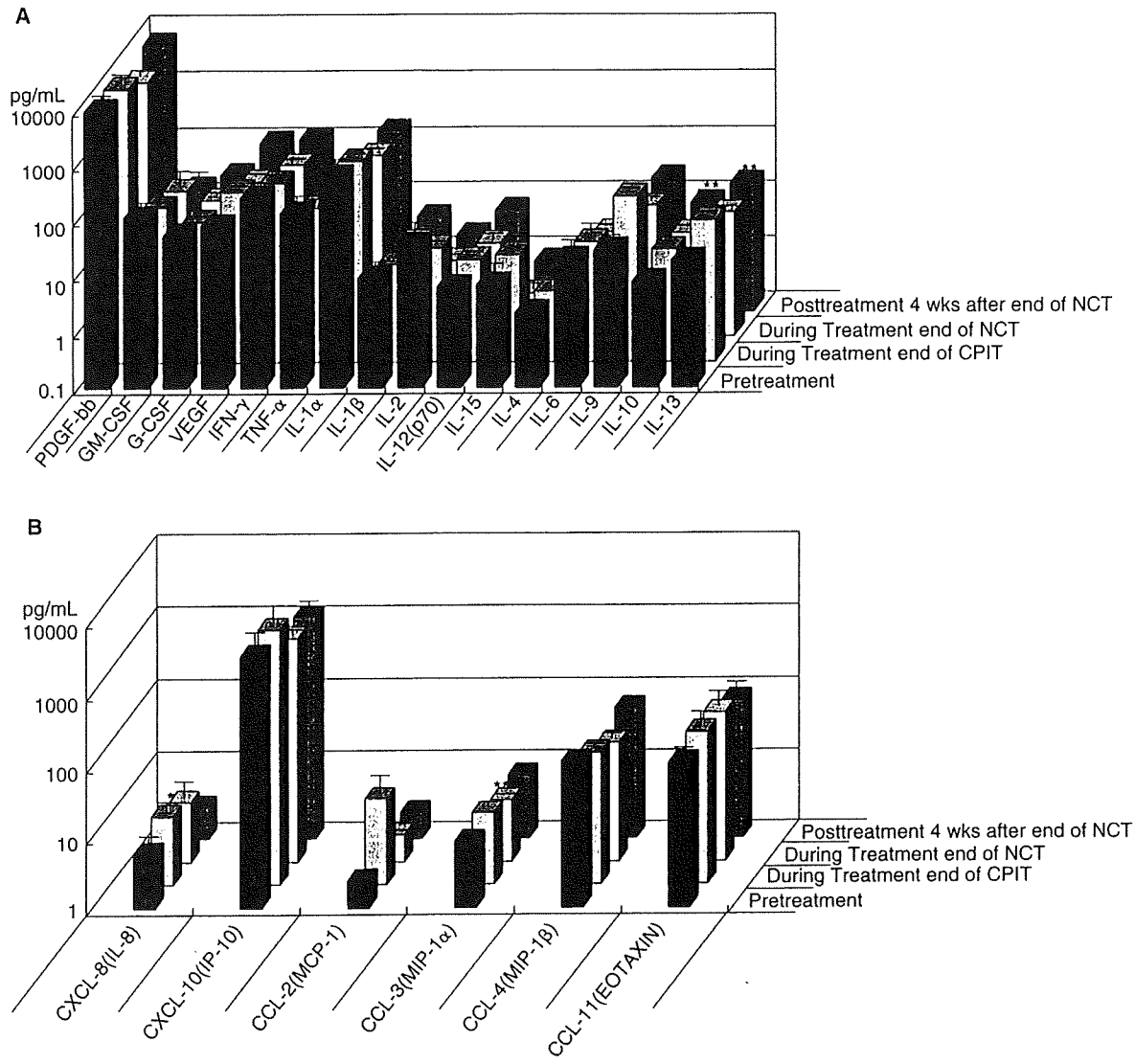

FIG. 4. Effect of RBV plus PEG-IFN-α2b using an "induction" approach with CPIT (NCT) on serum cytokines (A) and chemokines (B) in chronic hepatitis C patients with high viral load, genotype 1b (serotype I),and wild or intermediate type of ISDR (late virological responders). Significant difference: $^{*}P < 0.05$, $^{**}P < 0.1$. Abbreviations: RBV, ribavirin; PEG-IFN, pegylated interferon; CPIT, cyclic and periodic interferon treatment; NCT, novel combination treatment.

in CHC patients with high viral loads. Increased IFN-γ in serum suggested that CPIT improved immune responses to HCV. The resolution of HCV infections is associated with IFN-γ (Boni and others 2001; Sarin and others 2007). Functional alterations of HCV-specific T cells may be associated with persistent infection, including weak IFN-γ production, impaired proliferation, and an immature state of HCV-specific T cells (Spangenberg and others 2005). A persistent increase in serum 2′-5′-OAS levels induced by CPIT, which is downstream of IFN signaling, suggested that CPIT prevented the inhibition of IFN signaling by HCV.

To obtain initial virological clearance and the restoration of downregulation of innate immune response during the first part of the treatment, in addition to the direct inhibition of viral replication caused by CPIT, an immunomodulator such as RBV modulates antiviral immune responses that contribute greatly to the successful therapeutic immune response. RBV augments HCV-specific T-cell reactivity associated with augmented Th1 cytokines and suppressed Th2 cytokines (Chung and others 2008). RBV has marked effects on adaptive immune responses by augmenting Th1 cytokine production and inhibiting Th2 IL-4 production. RBV also lowered the numbers of Tregs and their associated cytokines, and this suggests another means by which adaptive immunity is promoted. Interestingly, the finding of restoration of STAT-1 patterns after RBV therapy back those seen in MHV-3-resistant animals, suggesting that RBV also alters innate immunity. Viral kinetic studies (Neuman and others 1998) during IFN-α therapy of CHC have defined two phases of viral decline: (1) a rapid, initial first phase, which is believed to reflect the antiviral efficacy of IFN-α; and (2) a delayed, slower second phase that is believed to reflect

TABLE 2. EFFECT OF RBV PLUS PEG-IFN-α2B USING AN "INDUCTION" THERAPY WITH CPIT (NCT) ON HEMATOLOGICAL STUDIES IN CHRONIC HEPATITIS C WITH HIGH VIRAL LOAD, SEROTYPE 1 (GENOTYPE 1B), AND WILD OR INTERMEDIATE TYPES OF ISDR

	Red blood cell ($10^4/\mu L$)				*Hb (g/dL)*				*White blood cell ($10^3/\mu L$)*				*Platelet ($10^4/\mu L$)*			
Patient No.	*Baseline*	*End of CPIT*	*End of NCT*	*24 weeks after the end of NCT*	*Baseline*	*End of CPIT*	*End of NCT*	*24 weeks after the end of NCT*	*Baseline*	*End of CPIT*	*End of NCT*	*24 weeks after the end of NCT*	*Baseline*	*End of CPIT*	*End of NCT*	*24 weeks after the end of NCT*
Early virological responders																
1	377	354	328	390	9.2	11.1	10.6	12.1	5.6	4.6	6.2	7.0	17.5	10.7	18.3	21.7
2	459	508	372	482	14.8	16.0	12.2	16.1	4.0	4.1	3.9	4.6	14.3	13.9	16.7	21.4
3	499	453	292	490	15.7	13.8	9.9	15.2	6.3	3.5	2.8	5.6	9.6	8.2	13.2	19.1
4	469	398	360	394	15.0	13.8	9.9	8.6	5.7	2.5	2.4	4.1	22.0	12.6	21.9	30.6
5	394	365	391	385	12.1	12.3	11.9	11.6	4.7	2.7	2.3	3.5	17.7	13.4	14.7	14.8
Late virological responders																
6	461	484	391	446	13.8	14.0	12.2	13.7	9.0	6.4	4.0	8.8	39.1	22.9	14.0	16.4
7	377	343	292	368	12.6	11.5	10.2	12.5	3.1	2.8	2.0	4.3	17.7	14.1	13.2	18.5
Mean ± SD	434 ± 50	425 ± 62	346 ± 43*	422 ± 50	13.3 ± 2.2	13.2 ± 1.7	11.0 ± 1.1*	12.8 ± 2.5	5.5 ± 1.9	3.8 ± 1.4*	3.3 ± 1.4*	5.4 ± 1.9*	19.7 ± 9.4	13.3 ± 4.6*	15.9 ± 3.3	20.4 ± 5.2
P-value (versus baseline)		$P = 0.5516$	$P = 0.0101$	$P = 0.627$		$P = 0.8536$	$P = 0.0530$	$P = 0.567$		$P = 0.0137$	$P = 0.00365$	$P = 0.0119$		$P = 0.0173$	$P = 0.3584$	$P = 0.185$

*Significant difference, $P < 0.05$.

Abbreviations: IFN, interferon; RBV, ribavirin; PEG-IFN, pegylated IFN; CPIT, cyclic and periodic IFN treatment; NCT, novel combination treatment.

the eradication of virus-infected hepatocytes. In several studies, RBV has been found to have little or no effect on the first phase of viral decline but does enhance the second phase particularly when the effectiveness of IFN-α is limited. Other mechanisms of action of RBV do not support the viral kinetic findings or lethal mutagenesis, but the possible effects of RBV on the TLR7 or IFN-α/β signaling pathways are alternative explanations that merit further evaluation (Chung and others 2008).

In addition, the combination of IFN-α and RBV increases antigen-specific CD4 T-cell proliferation and IFN-γ production by CD4 T cells (Barnes and others 2002). We investigated the efficacy, tolerance, and safety of CPIT as induction approach with virological clearance followed by RBV plus PEG-IFN-α2b (NCT) for seven difficult-to-treat CHC patients with genotype 1b, high viral load, and wild-type or intermediate type ISDR. In all cases, RVR and EVR were achieved without virological breakthrough. The SVR rate was correlated with the number of mutations in the ISDR (Watanabe and others 2001). Although three patients had wild-type and two patients had intermittent types of ISDR, they all achieved SVR (Table 3).

This study has shown that it is feasible to treat difficult-to-treat CHC patients with initial virological clearance induced by CPIT. Table 3 shows that NCT for difficult-to-treat CHC patients prevented virological breakthrough, leading to persistent, undetectable levels of HCV RNA resulting in a higher rate of SVR. Table 3 shows EAVR (5/7) with undetectable levels of HCV RNA before the end of CPIT showed SVR (5/7, 71.4%) among patients treated by NCT and LAVR (2/7) with undetectable levels of HCV RNA after the end of CPIT showed re-viremia after the end of NCT (2/7, 28.6%). NCT induced a significant decrease of serum hyaluronic acid, which is one of serum biomarkers for noninvasive measure of hepatic fibrosis, suggesting an improvement of hepatic fibrosis (Table 4). Paired biopsies were carried out in case 3 with SVR, and a reduction of fibrosis score from Stage F3 before NCT to Stage F2 15 months after completion of NCT was observed.

Multiple cytokine profiling of initial therapeutic response to IFN-α/RBV treatment in CHC patients showed that decreases in CCL-4, IL2, CXCL-8, and IL-1β correlated with the greatest drops in viral titer; decrease in IL-5, GCSF, and CCL-4 correlated with moderate drops in viral titer; and only CCL-2 correlated with the lowest drop in viral titer. Interestingly, the decrease in CCL-4 levels correlated with the decrease in viral titers in all patients (Wright and others 2005).

To assess the role of the host response in therapeutic outcome, we used a multiplex cytokine immunoassay to measure the therapy-induced changes among 22 serum cytokines. The current results showed (1) significant higher levels of CXCL-8, CXCL-10, and CCL-11, higher levels of IFN-γ, TNF-α, IL-1α, IL-2, IL-6, CCL-2, GM-CSF, G-CSF, and CCL-4, significant lower levels of IL-10 and IL-13, and lower levels of IL-12 and VEGF in EAVR compared to the controls at baseline before therapy; (2) significant higher levels of GMCSF, CXCL-10, and CCL-4, higher levels of IFN-γ, TNF-α, IL-1α, IL-1β, IL-2, IL-15, IL-6, IL-4, IL-9, CXCL-8, CCL-11, PDGF, and GCSF, and lower levels of IL-10, IL-12, IL-13, and VEGF in LAVR compared to the controls at baseline before therapy; and (3) an increase in cytokine levels including IL-12, IL-15, IL-10, and VEGF, and the downregulation of cytokines including IL-4, IFN-γ, TNF-α, G-CSF, and GM-CSF, and chemokines including CXCL-8, CXCL-10, and CCL-4 from baseline attributed to a better virological response to NCT.

Determinants of chronic infection include a low frequency of CTLs directed against a few HCV structural and NS proteins, and weak CD4+ T-cell proliferative response. These

TABLE 3. EFFECT OF RBV PLUS PEG-IFN-α2B USING AN "INDUCTION" THERAPY WITH CPIT (NCT) ON SERUM HCV RNA IN CHRONIC HEPATITIS C WITH HIGH VIRAL LOAD, SEROTYPE 1B (GENOTYPE 1B), AND WILD OR INTERMEDIATE TYPES OF ISDR

			HCV RNA in serum (KIU/mL)							
Patient No.	*Serotype*	*ISDR number of mutations in. NS5A gene*	*Baseline*	*4 weeks (RVR)*	*12 weeks (EVR)*	*24 weeks (end of CPIT)*	*72 weeks (end of NCT)*	*96 weeks (24 weeks after end of NCT)*	*Virological breakthrough*	*Outcome*
Early virological responders										
1	I	n.d.	1480	<5.0	(−)	(−)	(−)	(−)	(−)	SVR
2	I	Wild (0)	824	<5.0	(−)	(−)	(−)	(−)	(−)	SVR
3	I	Wild (0)	536	<5.0	(+)	(−)	(−)	(−)	(−)	SVR
4	I	Wild (0)	3600	<5.0	(+)	(−)	(−)	(−)	(−)	SVR
5	I	Intermediate (1)	770	<5.0	(−)	(−)	(−)	(−)	(−)	SVR
Late virological responders										
6	I	Intermediate (2)	>5000	<5.0	(+)	(+)(−)[§]	(−)(+)[§]	3400	(−)	TVR
7	I	Intermediate (1)	4400	<0.5	(+)	(+)(−)[¶]	(−)600[§] 4500[§]	850	(−)	TVR
Mean ± SD			2298 ± 1523	RVR 7/7	EVR 7/7	ETVR (CPIT) 5/7 cEVR (3/7)	ETVR (NCT) 7/7 pEVR (4/7)	SVR 5/7 TVR 2/7	Without BT 7/7	

(−) In HCV RNA, undetectable HCV RNA (< 50 IU/mL); (+) in HCV RNA, detectable HCV RNA (>50 IU/mL); [§]29 weeks of NCT; [§]4 weeks after end of NCT; [¶]30 weeks of NCT; [§]8 weeks after end of NCT; BT, breakthrough.

Abbreviations: ISDR, IFN sensitivity determining region; IFN, interferon; RVR, rapid virological response; EVR, early virological response; cEVR, complete EVR; pEVR, partial EVR; SVR, sustained virological response; TVR, transient virological response; CPIT, cyclic and periodic IFN treatment; NCT, novel combination; n.d., not determined.

TABLE 4. EFFECT OF RBV PLUS PEG-IFN-α2B USING AN "INDUCTION" THERAPY WITH CPIT (NCT) ON SERUM 2'-5' OAS AND HYALURONATE IN CHRONIC HEPATITIS C WITH HIGH VIRAL LOAD, SEROTYPE 1B (GENOTYPE 1B), AND WILD OR INTERMEDIATE TYPES OF ISDR

	2'- 5'OAS (pmol/mL)			*Hyaluronate (ng/mL)*			
Patient No.	*Baseline*	*End of CPIT*	*End of NCT*	*Baseline*	*End of CPIT*	*End of NCT*	*24 weeks after the end of NCT*
Early virological responders							
1	96.6	261	147	383	253	102	102
2	-	583	583	103	96	30	45
3	135	136	177	166	96	64	61
4	59	142	91	202	270	65	69
5	124	133	178	264	49	141	105
Late virological responders							
6	166	252	165	364	48	60	39
7	53	130	109	177	70	97	124
Mean ± SD	105 ± 44.4	233.9 ± 164.3*	207.1 ± 169.1*	237.0 ± 104.9	126.0 ± 94.7*	79.9 ± 36.2*	81.4 ± 36.8*
P-value (vs baseline)		$P < 0.05$	$P < 0.05$		$P < 0.05$	$P < 0.05$	$P < 0.05$

*Significant difference, ($P < 0.05$).
Abbreviations: CPIT, cyclic and periodic IFN treatment; NCT, novel combination treatment.

T-cell defects are associated and possibly related to a defect in the functions of both pDCs and mDCs. In addition, the increased proportion of Tregs contributes to the HCV-specific subversion of innate and adaptive immune responses in chronic HCV infection. Therefore, the expression and biological function of cytokines are critical in defining host response, as these mediators are principal regulators of the immune response. Cytokines are polypeptides produced mainly by cells involved in innate and adaptive immunity, and are powerful mediators of inflammation and microbial elimination. In particular, the cytokines produced during the innate immune responses have important roles in stimulating the subsequent adaptive immune responses and shaping the development of these responses. Chemokines recruit lymphocytes to the appropriate site of action at different stages of the adaptive immune responses. CC chemokines including MCP-1, RANTES, and MIP-β are chemoattractants not only for monocytes, but also for NK cells and CD45 RO+ memory-like T lymphocytes in human peripheral blood (Polyak and others 2001; Dahari and others 2005).

The engagement of PAMP receptors, including TLRs and the RIG-I-like helicase, following HCV and other RNA viral infections initiates signaling pathways that lead to the synthesis of IFN-α/β, TNF-α, IL-12, and IL-15. These are largely produced by mDCs and pDCs that express TLRs in abundance. IFN-α/β produced by DCs activates NK cells enhancing their cytotoxic potential and stimulating their production of IFN-γ.

Furthermore, IL-2, IL-12, and IL-15 activate NK cells (Gao and others 2008). IL-15 induced in APCs by IFN-α/β may in turn induce the selectively proliferation of CD44 cells indicating the importance of IFN-α/β–induced IL-15 production for the proliferation of T cells during viral infections. IL-15 is essential for the development of NK and NKT cells as well as for the differentiation of CD8+ memory T cells (Wertheimer and others 2007).

DC functions appear to play a major role in the immune response to HCV infection and may be deficient in patients with CHC. These results suggest that chronic HCV infection is associated with alterations in innate immune responses at multiple levels. IL-15 influences DC differentiation and mutation (Wertheimer and others 2007) and is produced by DCs themselves after exposure to proinflammatory stimuli. In humans, chronic HCV infection affects DC function in terms of impaired antigen presentation and altered cytokine production. Both DC differentiation and functional maturation seem to be altered in patients with chronic HCV infection and are associated with increased IL-10 and reduced IL-12 production by DCs. IL-10 has been shown to modulate DCs to induce T-cell anergy and decrease IL-12 production (Szabo and others 2006). A novel aspect of DC function is the induction of immune tolerance by the generation of the Tregs as defined by the ability of the CD4+ CD25+ FoxP3+ cell subset to suppress effector T-cell function in an antigen-specific, cell-contact, and partly cytokine-mediated manner. HCV persistence was associated with a reversible CD4+ T-cell mediated suppression of HCV-specific CD8+ T cells caused by exhaustion from continuous T-cell stimulation, the induction of T-cell anergy, and the induction of CD4+CD25+Tregs that inhibits the immune response (Szabo and others 2006). Pharmacological manipulation of IL-15 Ra-mediated signaling in human DCs may become a highly effective technique for boosting the elimination of invading pathogens (Wertheimer and others 2007).

In response to type I IFN, DCs are able to express the MHC class I–related chain gene A/B (MIC A/B) and activate NK cells following ligation of the NK receptor, NKG2D. NK cells are key components of the innate antiviral immune response as the first line of defense. NK-cell activation is regulated by DCs by the production of IL-12, IL-15, IL-18, or IFN (Szabo and others 2006). A close association between the resolution of HCV infections and NK cell activity has been demonstrated (Khakoo and others 2004). DC functions may be restored by antiviral therapy, and preliminary data indicate that the expression of TNF-α-related apoptosis-inducing ligands in NK cells may be associated with an EVR.

Thus, the level of pretreatment HCV-specific T-cell response appears to correlate with a better outcome of IFN-α-based therapy in CHC; however, the treatment itself may decrease these T-cell responses but restore other immune responses that may play an important role in the clearance of HCV (Chung and others 2008).

Furthermore, IFN-α/β induces chemokines in acute HCV infection, which recruit HCV-specific T cells to the liver. In contrast, in chronic infection, HCV-specific T-cell responsiveness was decreased during effective antiviral therapy. These findings suggest that exogenous IFN acts as an antiviral agent in chronic infection and implies that T-cell responsiveness in established infection is antigen-driven (Chung and others 2008).

HCV may also be able to modulate antiviral responses in the host through interactions with elements of the inflammatory response. Among its many activities, IRF-3 regulates the expression of CXCL-8. HCVRNA and infection both induce CXCL-8 transcription via RIG-I and IPS-1, a process that involves the recruitment of IRF-3 to the CXCL-8 promoter.

Moreover, RIG-I stabilizes the CXCL-8 mRNA via AU-rich elements in the 3'-untranslated region of the mRNA. A working model proposes that the initial activation of the innate antiviral response during HCV infection also induces the expression of inflammatory cytokines and chemokines. During HCV-mediated blockade of dsRNA-induced antiviral responses, inflammatory mediators may still be expressed via the activation of other key transcription factors such as NF-κB, which is activated by many signaling pathways. These mediators may act to downregulate IFN-α/β responses (Chung and others 2008).

The current results (Figs 2-4) show that (1) IL-15 was increased at the end of CPIT in both EAVR and LAVR, serum CXCL-8 was significantly decreased in EAVR but not in LAVR during NCT; and (2) the levels of IL-12 increased significantly and CXCL-8 decreased significantly after the end of NCT in EAVR but not in LAVR. Importantly, the current study suggested that initial early virological clearance induced by CPIT before the use of a combination of RBV and PEGIFN-α2b induced the restoration of DC function and improvement of activation of NK cells indicated by the upregulation of IL-12 and IL-15, and the downregulation of CXCL-8, which suggested improvement in the innate immune response.

In previous studies, dose reductions or treatment discontinuations of PEG-IFN-α that were often required to manage adverse hematological events have been associated with a reduction in therapeutic efficacy (Manns and others 2001; Mughes and others 2006). In NCT, no serious adverse effects (AEs) were found, and the good tolerance of NCT was confirmed by the high compliance rates. Indeed, the results observed in this study agree favorably with other findings on the safety of IFN-β treatment in patients with CHC and support the use of nIFN-β as a safe and alternative option.

In conclusion, this study has shown that NCT achieved the prevention of viral escape and breakthrough resulting in persistent viral clearance of HCVRNA leading to the improvement in the innate immune response, and it is feasible to treat difficult-to-treat CHC patients with genotype 1b, high viral load, and wild or intermediate types of ISDR using RBV plus PEG-IFN-α2b with an "induction" approach, and initial virological clearance induced by CPIT resulting in an overall improvement in HCV outcome with SVR, SBR, and improvement of serum hyaluronic acid as a biomarker for hepatic fibrosis. Because of the improved response rate, the benefit of NCT is mostly achieved in difficult-to-treat CHC patients with HCV genotype 1b and a high baseline HCV RNA level. The findings from this study support the concept that viral clearance early in the course of therapy is linked to improved efficacy and reduced virological resistance, suggesting that agents providing the greatest viral suppression leading to EVR may be preferable as the initial early induction approach. An initial viral clearance induced by more adequate CPIT before beginning RBV plus PEG-IFN-α2b therapy may result in a higher rate of SVR in difficult-to-treat CHC patients with genotype 1b and high viral load. Considering the high proportion of patients cured in this study, additional studies would be of great value to further evaluate safety and viral efficacy in a controlled manner.

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＜原　著＞

慢性肝疾患患者を対象とした肝臓病教室での情報提供に対する医療者および患者の意識調査に関する検討

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要旨：関西22病院にて肝臓病教室に関するアンケート調査を行なった．対象は，医療者55名，慢性肝疾患患者176名．肝臓病教室を定期開催しているのは7施設，経験はあるが現在未施行2施設，未施行13施設であった．継続できない理由は，マンネリ化や慣れたスタッフの配置換えによるパワーダウン，教室の効果を把握しにくいなどで，開始できない理由は，準備などの時間がないが最も多かった．医療者と患者とも，各々95%，94%が教室は必要と回答した．提供すべき情報は，医療者は1位：肝臓病とは，2位：治療方法，3位：合併症とその対策/肝臓の働き，患者側は1位：治療方法，2位：治療効果，3位：食事療法を上位に挙げた．教室のメリットは，両者とも1位：自己管理の向上，2位：治療に対して前向きな姿勢になれる，3位：不安の軽減，と一致した．有効な患者教育の普及のためには，方法論の普及，有用な情報の種類や提供方法の検討，情報提供による効果の評価方法を確立し医療者のやる気の維持につなげるなどが必要と考えられた．

索引用語：　患者教育　　チーム医療　　コメディカル　　メンタルサポート

はじめに

慢性肝疾患患者の診療においては，ウイルス性慢性肝炎に対するインターフェロン治療や肝臓癌に対するラジオ波治療など患者にとっては侵襲性の高いものが多いが，患者はその治療選択を外来にて迫られることも多い．外来での短い診療時間で伝えられる情報は一般に十分とは言えず，患者には情報不足という負担があり，また実際治療選択に迷うことも少なくない．その欠点を補う目的で，肝臓病教室などが各施設で行われてはいるが，未だ一般的に施行されているとはいい難い．加藤らは全国医療機関に行なったアンケート結果より，2003年から2004年時点で肝臓病教室を開催しているのは約70施設弱であることを報告している[1)]．高血圧患者や糖尿病患者などでは，薬物療法以外の患者教育によって慢性疾患のコントロール状態を改善させることが指摘されているものの[2)3)]，慢性肝疾患での検討は極めて少ない．

我々は肝臓病患者への情報提供の有り方について検討を加える目的で，2005年より関西肝臓病教室アドバイザリーカンファレンスを立ち上げ，多施設で年1回研究会を行っている．今回，本研究会に参加した22医療機関において医療関係者と通院患者に選択肢を主としたアンケートを行い，肝臓病教室施行の現状を把握するとともに，患者と医療関係者の意識の比較を検討し，今後の方向性を考察したので報告する．

対象と方法

2006年1月から2月にかけて，関西肝臓病教室アド

1）大阪厚生年金病院内科
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1.本アンケート結果を紙面もしくは口頭で発表することに同意頂けますか？(はい、いいえ)
2. あなたの病気は　どれにあたりますか？
(慢性肝炎、肝硬変、肝臓癌、脂肪肝、自己免疫性肝炎、肝臓が悪いことしかわからない、その他)
3. 貴施設では肝臓病教室を定期的に開催していますか？(はい、いいえ)
はい→年間何回くらい開催していますか？　(　　)回 / 年
→肝臓病教室に参加したことがありますか？
いいえ→他施設の肝臓病教室や市民公開講座に参加されたことがありますか？

4. 肝臓病教室は有用だと思いますか？(はい、いいえ)

5. 肝臓病教室においてどのような情報が知りたいですか？上位より5つあげてください。
① 肝臓の働き　② 肝臓病とは　③ 肝臓病の治療方法
④ 肝臓病の治療効果　⑤ 合併症とその対策　⑥ 治療費
⑦ その筋の専門家の意見　⑧ 治療体験者の意見　⑨ 食事療法
⑩ 薬の知識　⑪ 家庭での注意点　⑫ 運動療法
⑬ 検査の意味すること　⑭ 患者会の情報　⑮ 本の紹介
⑯ その他(できるだけ詳しくご記入ください)

6. 肝臓病教室に参加するメリットは何だと思われますか？上位より5つあげてください。
①病気に対するセルフケアが向上する　②治療へ前向きになれる
③他の患者さんと仲良くなり、情報交換の場となる　④患者さんと医療者のコミュニケーションの場ができる
⑤病気に対する不安の軽減となる　⑥診察でわからなかった点をおぎなえる　⑦その他

7. 肝臓病教室について自由にご記入ください。

b

1. 本アンケート結果を紙面もしくは口頭で発表することに同意頂けますか？(はい、いいえ)
2. 職種を教えてください
(医師、看護師、栄養士、薬剤師、検査技師、その他)
3. 貴施設では肝臓病教室を定期的に開催していますか？　(はい、いいえ)
はい→年間何回開催していますか？　(　　)回 / 年
→あなたは肝臓病教室に参加していますか？
いいえ→過去に開催した経験がありますか？
→今後開催する予定がありますか？
4. 肝臓病教室は有用だと思いますか？　(はい、いいえ)

5. 定期的に肝臓病教室を開催するために特に必要なことはなに何だと思いますか？
(上位より5つ)
①スタッフの熱意
②肝臓病教室開催に対する診療報酬
③肝臓病教室を実施するためのコスト(資料の作成にかかるコストなど)
④病院側の理解または協力
⑤スタッフが肝臓病教室の準備や開催に関わる時間
⑥肝臓病教室を開催する場所
⑦肝臓病教室を開催するための知識
⑧教材
⑨その他(できるだけ詳しくご記入ください)

6. 肝臓病教室において患者さんにどのような情報を提供すればよいと考えますか？(上位より5つ)
①肝臓の働き ②肝臓病とは ③肝臓病の治療方法 ④肝臓病の治療効果 ⑤合併症とその対策 ⑥治療費
⑦その筋の専門家の意見 ⑧治療体験者の意見 ⑨食事療法 ⑩薬の知識 ⑪家庭での注意点 ⑫運動療法
⑬検査の意味すること ⑭患者会の情報 ⑮本の紹介 ⑯開発中の薬剤 ⑰治験の情報
⑱その他(できるだけ詳しくご記入ください)

c

7. 肝臓病教室を開催するメリットは何だと思われますか？(上位5つ)
①患者さんへの情報提供ができ、セルフケアが向上する　②患者さんへの情報提供ができ、患者さんが治療へ前向きになる
③患者さん同士が仲良くなり、情報交換の場となる　④患者さんと医療者のコミュニケーションの場ができる
⑤患者さんの病気に対する不安の軽減となる　⑥患者さんへの情報提供ができ、診察時間の説明不足を補える
⑦スタッフの知識が向上する　⑧コ・メディカルの連携がよくなる　⑨その他

8. 肝臓病教室の1番の目的は何でしょうか？(ひとつ選んでください)
①診療効率アップ　②患者と医療者の意思の疎通　③チーム医療の確立　④地域への貢献　⑤その他

9. これから肝臓病教室を開催する施設の方が心配している一番の障壁は何でしょうか？(ひとつ選んでください)
①準備や開催の時間がないこと　②コ・メディカルの協力が得られないこと　③会場・場所が施設内に準備できないこと
④スライドなどの教材が作成できないこと　⑤その他

10. 現在開催しておられる施設では肝臓病教室を継続するのに障壁は何でしょうか？(ひとつ選んでください)
①マンネリ化　②スタッフの配置換え　③患者さんが集まらない　④やる気の持続　⑤効果が確認できない　⑥その他

11. 肝臓病教室に関して自由にご記入ください。

Fig. 1　1a, Questionnaires for patients. 1b, Questionnaires for medical staff. 1c, Questionnaires for medical staff.

バイザリーカンファレンスに参加した22施設(大阪厚生年金病院，国立病院機構大阪医療センター，北野病院，岸和田徳洲会病院，済生会中津病院，NTT西日本大阪病院，市立池田病院，青樹会病院，大阪回生病院，大手前病院，関西医科大学附属病院滝井，関西医科大学附属病院枚方，大阪警察病院，市立豊中病院，住友病院，大阪鉄道病院，日生病院，大阪日赤病院，大阪大学附属病院，東大阪市立総合病院，松下記念病院，淀川キリスト教病院）において無作為に抽出した医療者および通院の慢性肝疾患患者に以下のアンケートを依頼した．医療者55名（看護師21，医師14，栄養士10，薬剤師8，検査技師1，医療秘書1）と通院している慢性肝疾患患者176名（慢性肝炎121，肝硬変26，肝臓癌8，アルコールなどその他の疾患が14，無記名7）から回収を得ることが出来，回収率は90%以上であった．

実施したアンケート内容をFig. 1(a-c)に示す．医療者，患者別に配布し無記名で回収し，解析を行なった．この中の一部のアンケートでは医療者と患者に対して同じ質問を実施した．選択肢から上位5つを挙げてもらうものに関しては，1位を5点，2位を4点，3位を3点，4位を2点，5位を1点と点数化し，集計した．医療者と患者に対して同じ質問をしたアンケートに関しては，各項目についての点数をMann-Whitney U検定を行なうことで比較し，p値が0.05以下の場合，有意差があるとした．またアンケートをとる際に，内容を紙面や口頭で発表することの承諾を得た．

結　果

肝臓病教室を定期的に開催している施設は22施設中7施設(32%)で，開催していない施設は15施設(68%)であった．未施行15施設のうち，経験の有無については，経験ありが2施設(13%)，経験無しが13施設(87%)であった．また，今後の開催予定については，未施行15施設回答中3施設（20%）のみが開催予定ありで，12施設は開催予定が無いと回答している．教室を開催した，もしくは参加した経験は，医療者で33%，患者で48%であったが，参加の有無は関係なく，それぞれ95%と94%で教室は有用と考えていた．

提供すべき情報を重要なものからあげてもらった所，医療者は，1肝臓病とは，2治療方法，3合併症とその対策，3肝臓の働き，5食事療法の順であったが，患者側は，1治療方法，2治療効果，3食事療法，4合併症とその対策，5薬の知識であった(Table 1)．肝臓の働き，肝臓病についての2項目は，医療者側の点数が有意に高く，治療方法，治療の効果，専門医の意見については，患者側の点数が有意に高かった．肝臓病教室のメリットについては，両者とも1．自己管理の向上，2．治療に対する前向き姿勢になれる，3．不安の軽減，と上位3項目に一致が見られ，これら上位には点数にも有意差は見られなかったが，患者の疑問に対して補える，や患者同士のコミュニケーションになるなどの下位の項目には有意差が見られた（Table 2)．

Table 1 Information dissemination desired by patients and medical staff

	Patients	Medical staff	p
Liver function	0.39±1.24	1.53±2.06 (3)	< 0.01
Liver disease	0.49±1.36	3.67±1.89 (1)	< 0.01
Methods of treatment	3.32±2.10 (1)	2.62±1.80 (2)	< 0.01
Effects of treatment	2.88±1.91 (2)	1.26±1.43	< 0.01
Adverse effects and their management	1.19±1.62 (4)	1.53±1.67 (3)	NS
Medical fees	0.48±1.13	0.07±0.26	NS
Opinion of specialists	0.86±1.45	0.07±0.38	< 0.01
Opinion of patients	0.56±1.08	0.24±0.69	NS
Dietary care	1.22±1.56 (3)	1.06±1.28 (5)	NS
Drug information	1.05±1.37 (5)	1.03±1.40	NS
Health care at home	0.79±1.36	0.80±1.24	NS
Exercise	0.39±0.85	0.31±1.15	NS
Medical examination	0.67±1.23	0.29±0.76	NS
Patients' circle	0.11±0.43	0.09±0.35	NS
Medical books	0.02±0.15	0.04±0.27	NS

Values are expressed as mean±standard deviation. Patients and medical staff scored the items from 5 to 1 with 5 indicating the highest level of importance. The sum points of each factor are presented. Rankings are expressed in parentheses.
NS, not significant.

Table 2 Merits of holding classes on liver disease. Comparison of concepts of patients and medical staff

	Patients	Medical staff	p
Improvement of self-care	3.44±1.84 (1)	3.42±1.78 (1)	NS
Active acceptance of treatment	3.11±1.71 (2)	3.38±1.76 (2)	NS
Communication between patients	0.63±1.28	1.18±1.43	< 0.01
Communication between medical staff and patients	1.29±1.49	1.84±1.73	NS
Reduction of anxiety	2.42±1.58 (3)	2.09±1.74 (3)	NS
Responses to patients' questions	2.07±1.62	1.51±1.81	< 0.05

Values are expressed as mean±standard deviation. Patients and medical staff scored the items from 5 to 1 with 5 indicating the hjghest level of importance. The sum points of each factor are presented. Rankings are expressed in parentheses.
NS, not significant.

医療者側に教室の最も重要な目的を聞くと，患者と医療者の意思の疎通のためが54％で，その次にチーム医療の確立が19％で，診療効率のアップは11％と3番目であった(Fig. 2)．開催しても継続できない理由として，マンネリ化や慣れたスタッフの配置換えなどによるパワーダウン，教室の効果が分りにくいことややる気が持続しないことなどが挙げられており，未経験の施設が教室を開始できない理由としては，準備や開催の時間がないというのが77％と最も多い理由であった (Fig. 3a-b)．教室の持続に必要なものを医療者に尋ねると，医療者の熱意と準備や開催にかかわる時間がともに21％で，ついで病院側の理解や協力が19％，実施するための知識（17％）や費用（6％）などであった (Fig. 4)．

考　察

今回の検討では，慢性肝疾患患者に対する情報提供(肝臓病教室)について，医療者，患者とも殆どが必要

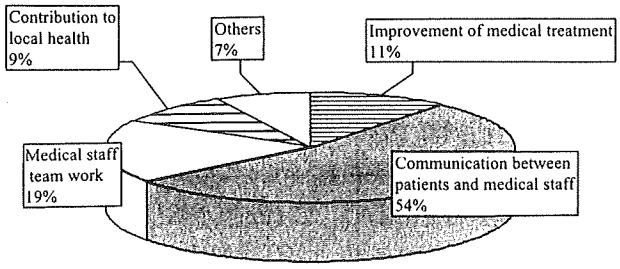

Fig. 2 Most important aim of classes on liver diseases from the viewpoint of the medical staff. Each medical staff member selected one factor as the most important. The numbers of those who chose each factor were compared and expressed as %.

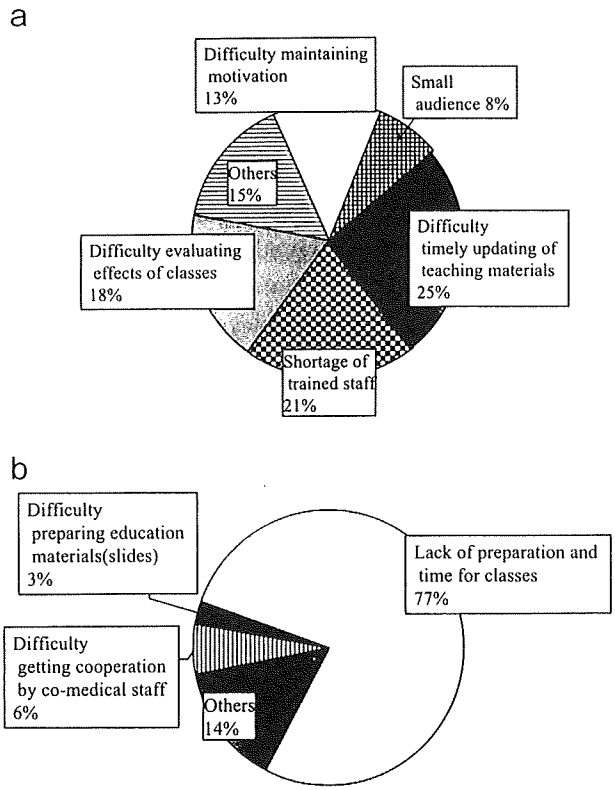

Fig. 3 3a, Factors interfering with the holding of classes regularly. 3b, Factors interfering with the starting of classes. Each medical staff member selected one factor as the most important. The numbers of those who chose each factor were compared and expressed as %.

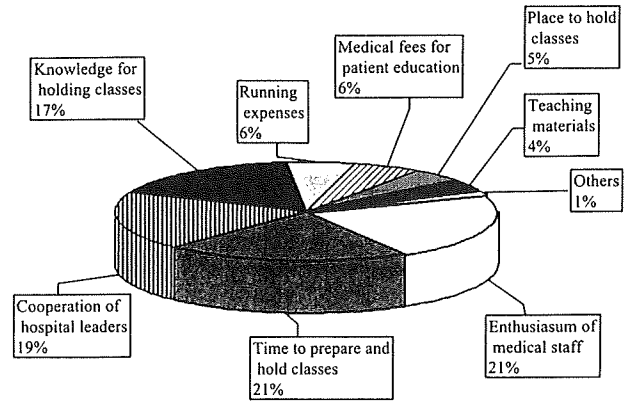

Fig. 4 Factors considered necessary for having medical classes on liver disease from the viewpoint of the medical staff. Factors were scored from 5 to 1 with 5 indicating the highest level of importance. The sum points for each factor were compared and expressed as %.

であると考えていることが分った．その理由として，両者とも教室のメリットに，自己管理の向上や治療に前向きになる，さらには不安の軽減などを上位に挙げており，日常診療だけではこれらの要因に対して十分満足できていないことが考えられる．我々は，慢性肝疾患患者に対して，日常診療特に外来診療において，ウイルス性慢性肝炎に対するインターフェロン治療や肝臓癌に対する治療など侵襲性の高い治療の施行を決定しなければならないことが多い．さらに，短い外来診療時間の中で十分な情報を患者に伝え，またメンタル面のサポートもした上で，その効果と危険性について十分なインフォームドコンセントを取っていくことの困難さが背景にある．また医療者側の意識として，教室の目的の一番が患者と医療者の意思の疎通を挙げており(54%)，診療効率のアップが3位(11%)であったことは，医療者が患者との意思の疎通を重視している現状が分かり興味深い．

Nagao ら[1]は，地域の病院（肝臓専門医）と開業医(肝臓非専門医)とそこに通院する患者達に1対1のアンケートを行い，インターフェロン治療を勧められた139名のC型慢性肝炎患者のうち，治療を受け入れた患者の割合を，治療を勧めた医師の専門の有無によって比較している．それによると，肝臓専門医より勧められた場合の患者のインターフェロン受療率は86%だったのに対し，非専門医から勧められた場合は34%であったと報告しており，患者が治療法を選択する上で，新しく，かつ正確な知識や情報を提供することが重要な要素であることを示唆している．同じ検討の中で，女性の方が男性よりも合併症に対する不安が強く(33.3% vs 18.2%)，治療導入の障壁になっていることも示している．検査や治療に際し，事前の正確な情報提供が患者の症状の軽減や薬物への依存を減らす要因であるこ

とは，狭心症の疑いの患者における検査でも指摘されている[5]し，また糖尿病や高血圧の管理においても，適切な情報提供が通常の医療の効果を上げることが指摘されている[2][3]．今後，慢性肝疾患に対する情報提供について具体的な効果を明らかにすることが課題といえる．

情報提供の方法としては，通常の診察時間内に医師から直接情報を提供したり，疾患に関するパンフレットを渡すなどがあるが，そのいずれもが現状では十分とは言えない．そこで，患者に対する集団指導という形をとる肝臓病教室を施行しているわけであるが，これについて当研究会に参加し，教室に興味を持っている施設であっても定期的に開催しているのは，7/22（31.8％）であった．定期的に開催していない15施設のうち，2施設については，経験はあるが継続できていなかった．開催できない理由としては，準備をしたり開催する時間が無いというものが一番多かった．ゼロからの準備は確かに困難を伴うものであるが，肝臓病教室そのものに関する論文[6][7]や，単行本[8]なども出版されており，そのような教材を普及させていくことがひとつの対策にはなるであろう．継続できない理由としては，マンネリ化，スタッフの配置換え，教室の効果の確認が出来ない，やる気を継続できないなどが上げられている．前述したように，正しい知識を患者にもってもらうことは，治療方針の決定や自己管理に際し有用であると想像されるが，そのことを実証した報告は現段階ではほとんど見られない．肝臓病教室を実施している多くの施設では，終了後にアンケートを行い，今後の改善点を検討しているにとどまっている．肝臓病教室を中心とした患者への情報提供の試みによって，前述した問題点がどのくらい改善されるのかなどを検討しながら，教室の意義を明らかにすることが，スタッフのやる気を上げたりスタッフの配置換えや病院からの経済協力につながると考える．

提供すべき情報の種類に関しても，今回のアンケートでは医療者と患者側で，食い違いが見られた．医療者は，肝臓の働きや病気のしくみなど基本情報に対する優先度が患者よりも有意に高く，病気のしくみなどを含めて医療を理解してもらおうと考えているのに対し，患者側は治療方法やその効果など，即戦力的な知識に対する優先度が医療者に比べ有意に高かった．これに関しても，治療効果や患者の自己管理の効率を上げるためには，どんな情報が有効かについての検討が少ないため，どちらの希望の方が有効かは，現時点では不明である．Jeffreyらは，過敏性腸症候群の患者達に対する認知行動療法の有効性を指摘している[9]．認知行動療法とは，物事やストレスに対する考え方を教育していく生活指導であり，一種の心理療法でもある．また癌などの慢性疾患を持っている患者は，多くが心理的な問題を抱えており，これが診断や正確な治療の妨げになる場合があるが，これに対する系統的な取り組みは殆ど見られない[10]．しかし臨床心理の専門医師ではなく，心理サポートの訓練を受けた看護師が補助することで，抑うつスコアだけでなく，倦怠感や不安などの改善効果が見られるという試みも報告されている[10]．一口に肝臓病教室と言っても，慢性肝炎，肝硬変から肝臓癌まで疾患の幅があるため，提供すべき情報や支援の種類も多岐に亘る．結果として通常の医療の効果をサポートし，患者のQOLを上げるものを検討していかなくてはならないが，そのためには，効果を評価する尺度を何にするかという問題も重要となる．今後は，通常の医療行為に加えて，患者への情報提供や支援のあり方にも注目して検討を加えていく必要があると考えられる．

今回の検討対象は，症例数が少ないこと，医療従事者の職種が多彩なこと，また患者の疾患重症度も異なることなどがあり，これらの因子がアンケート結果に偏りを与えている可能性も否定は出来ないため，これらの因子による影響は今後の検討課題である．

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Viewpoints on the providing of information about liver disease to patients with chronic liver disease in classes on liver disease

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Medical staff (55) and out-patients (176) of 22 hospitals in Osaka were asked to respond to questionnaires about educational classes on liver disease. In seven hospitals, such classes were held regularly, but not in fifteen. Factors interfering with the holding of classes regularly were lack of motivation, shortage of trained staff, and lack of preparation time. However, 95% of the medical staff and 94% of the patients thought such classes to be useful for self-management, promotion of the active acceptance of treatment, and reduction of anxiety. The most important information provided was considered by the medical staff to be 'knowledges about liver disease', while the patients chose 'methods of treatment'. These findings point to the need to develop an effective method for the education of patients with chronic liver disease.

Key words: education of patients　team work of medical staff　co-medical staff　mental support

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特集 B型肝炎—病態解明と治療の最前線

2 B型肝炎の治療最前線 (7) B型慢性肝炎に対する強化ワクチン療法

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Key words: ワクチン療法，細胞性免疫，HBs抗原，インターフェロン，核酸アナログ剤

要 旨

B型慢性肝炎の治療は，現在インターフェロンと核酸アナログ剤による抗ウイルス療法が主体であるが，治療を終了すると再燃が多いこと，核酸アナログ剤を長期に使用すると耐性株が出現してくるなどの問題がある．細胞性免疫は，ウイルス増殖を抑制するうえで重要な働きをしているが，HBVワクチンは，その細胞性免疫を賦活することで，ウイルス増殖を抑制できる可能性がある．単独での効果は弱いが，核酸アナログ薬との併用や強力なアジュバントの開発，樹状細胞を用いた検討などが行われている．われわれは，ワクチン投与頻度と期間を増やす強化ワクチン療法を臨床検討しており，一定の効果を上げることができている．

I．B型慢性肝炎の免疫療法とワクチン療法

この項のポイント
- B型慢性肝炎でウイルス増殖を抑えるためには，生体の免疫応答を上げることが重要であり，ワクチン療法は，免疫応答を促進する治療の一つになる可能性がある．

B型慢性肝疾患の治療目標は，B型肝炎ウイルス(HBV)の増殖を持続的に抑制することで，肝炎を沈静化させ，肝病変の進展や合併症の発現を抑えることである．

現在，治療の主体はインターフェロン(IFN)と核酸アナログ剤であり，その成績は一定の効果を上げているものの未だ満足できるものではない．IFN治療は，治療中の副作用の問題や治療後の再燃率が高いという問題があり，核酸アナログ剤は治療の中断による再燃率が高いため，治療の継続が基本となるが，それにより耐性株が出現してくることが問題点である[1]．そこで免疫賦活治療により，ウイルスに対する免疫反応を十分に増強することができれば，ウイルス増殖を抑制でき，また不十分でもIFNや核酸アナログ剤による治療効果を上げたり，再燃を起こさずに抗ウイルス治療を中止できる可能性が考えられ，種々の免疫促進治療が検討されている[2]．

Polらが，HBs抗原を用いたワクチンをB型慢性肝炎の患者に月1回の頻度で投与し，ウイルス増殖が抑制できる例があることを示した[3]のは，感染予防薬であるワクチンが，ウイルスキャリアに対する免疫賦活治療薬になりうることを示した貴重な報告となった．その後，核酸アナログ剤とワクチンを併用することにより，HBe抗原のセロコンバージョン率が改善する

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という報告や，有意差はないが核酸アナログ剤に対する耐性株の出現率が低下するという報告などが示されている[4)~6)]．ただ，多くがワクチンを月1回投与する方法を用い，投与期間を6カ月程度に限定しており，治療効果も十分とはいえない．そこでわれわれは，ワクチン投与の頻度と期間を増やすことで免疫増強効果を上げる可能性を期待し，ワクチンを毎週もしくは隔週投与する強化ワクチン療法をパイロット研究として施行した．

Ⅱ．B型慢性肝炎に対する強化ワクチン療法の検討

この項のポイント
- 従来のB型慢性肝炎に対するワクチン療法(月1回，6カ月投与)の効果は，十分とはいえないため，ワクチン投与回数，投与期間を増やす強化ワクチン療法の効果を検討した．
- ワクチン療法を中心とする免疫治療は，さらに工夫することで，単独もしくは抗ウイルス治療との併用治療効果をさらに上げられる可能性がある．

1．対象と方法

B型慢性肝炎26例を以下の2群に分け，ワクチン投与の効果を検討した．

A群：肝機能異常の持続する20例に対し，HBVワクチン1バイアル(10 μg，明乳乳業株式会社)を1回/1～2週筋肉内投与下にIFN(HLBI 6MUもしくはIFNα2b 6MU)を6カ月投与した．同意の得られた17例ではエンテカビル(0.5 mg/day)もしくはラミブジン(100 mg/day)を約3～4カ月併用投与した．これら核酸アナログ薬は，治療効果に関わらずIFN投与終了の1カ月前には終了した．ワクチンは，IFN終了後も継続投与とした．効果判定は，抗ウイルス治療後6カ月間，HBV-DNA＜5.5 LGE/m*l*かつALT＜40 IU/*l*を持続するものを有効とし，それ以外のものを無効とした．

B群：肝機能異常が軽微なため，IFNなど抗ウイルス治療の効果が期待できない症例や抗ウイルス剤拒否の6例とA群の再燃例2例，合計8例にワクチンを単独使用(7例)・またはSNMCと併用投与した(1例)．効果判定は，ワクチン投与中，ウイルス量が1 log以上低下するか，単独投与にて肝機能異常を認めなくなった症例を有効とし，ワクチン投与中ウイルス量増加による肝炎の増悪例を無効とした．また5例で，ワクチンを減量もしくは中止し，その後の経過を追跡した．本研究は，大阪厚生年金病院で行い，すべての患者より文書での承諾を得，倫理委員会の承認を得て行った．

2．結　　果

1) IFN併用強化ワクチン療法(A群)

治療前後のHBV-DNAとALT値の推移を**図1**に示す．HBe抗原陽性は13例で，治療中に46%の6例でHBe抗原の消失がみられたものの，3例で抗ウイルス治療後に再燃，最終的にHBe抗原陰性が持続した例は3例であった．最終的に有効例と判定されたのは7/20例(35%)であった．治療効果に影響を与えた因子を解析すると(**表**)，治療前のHBV-DNAの値が有効例で有意に低値であったが，その他年齢，性別，HBe抗原・抗体には有意差は認めなかった．有効例の1例を示す(**図2**)．ワクチンを隔週投与下に，HLBI 6MU週3回投与を開始．HLBI投与2カ月目，HBV-DNAの低下が遅く，ラミブジン100 mg/dayを追加投与．HBV-DNAが測定感度以下になって安定した5カ月目にラミブジンを中止し，その後HLBIも中止したところ，HBV-DNAが漸増したため，HLBI終了後2カ月目よりワクチン投与の回数を週1回に増量したところ，HBV-DNAが増加しなくなり，有効例となった．

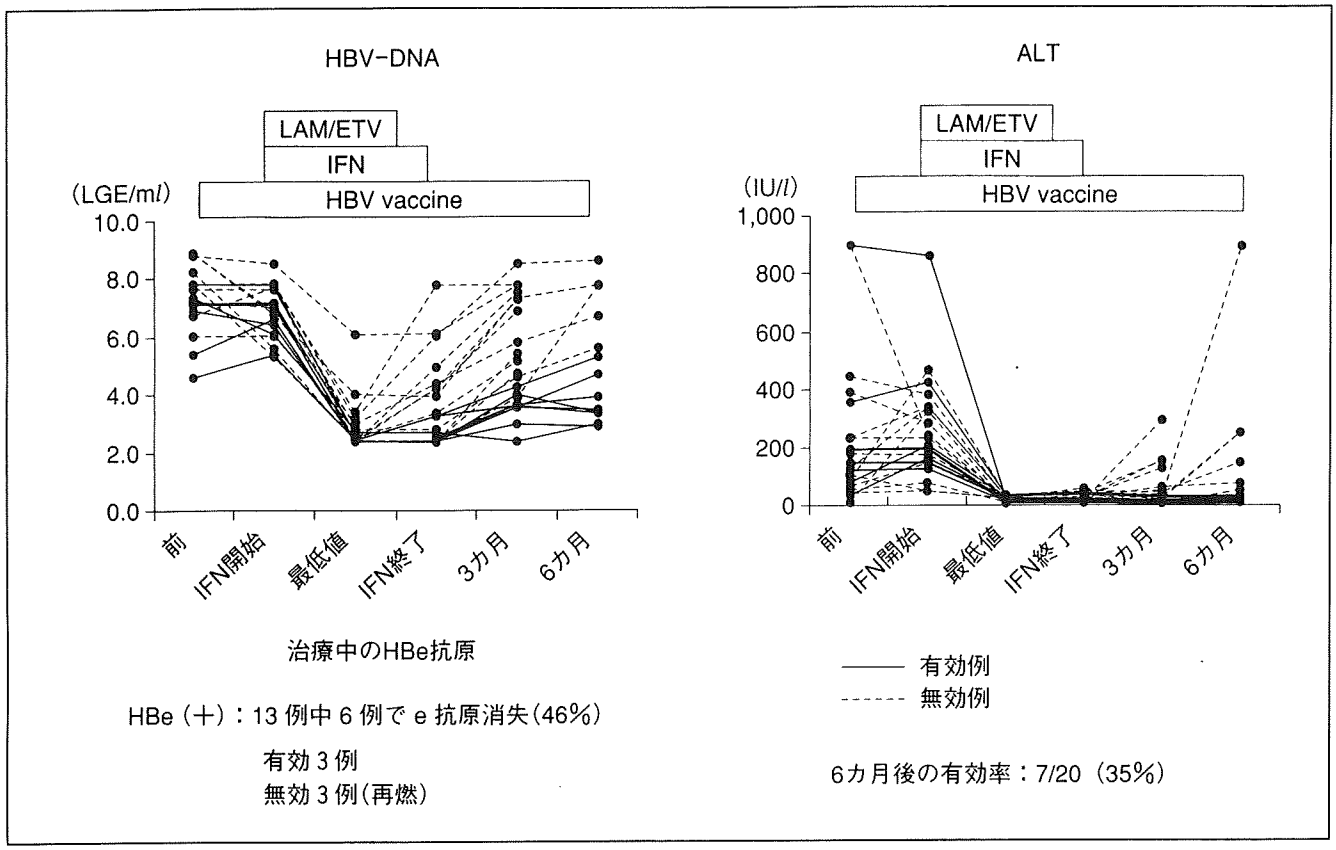

図1　Group Aにおける治療前後のHBV-DNA，ALTの経過

表　患者背景と治療効果（Group A）

	治療効果		P
	有効	無効	
N	7	13	
Age (yo)	43.4±9.0	37.6±10.3	0.302
M/F	5/2	7/6	0.444
T. Bil (mg/dl)	0.9±0.2	0.9±0.3	0.476
AST (IU/l)	132.7±96.8	141.6±121.5	0.968
ALT (IU/l)	268.7±292.2	246.8±250.1	0.905
Alb (g/dl)	3.9±0.3	4.1±0.4	0.219
HBeAg＋/－	3/4	10/3	0.130
HBV-DNA (LGE/ml)	6.66±1.18	7.77±0.77	0.026

2）強化ワクチン療法（単独もしくは肝庇護療法併用）（B群）

HBV-DNAの推移を**図3**に示す．8例中5例でALTの安定およびHBV-DNAの低下傾向より有効と判定した．残りの3例では，HBV-DNAの増加を伴うALTの上昇があり，無効と判定した．

有効例の1例を示す（**図4**）．他院でIFN治療を施行するも再燃・軽快を繰り返すために当院へ紹介された．ワクチンとIFNを併用する目的で，ワクチン隔週投与を開始したところ，ALTの低下とともにHBe抗原の低下も認めた