[7,8]. There is a more pressing need for the establishment of new and more active treatment strategies that are superior to conventional TACE to improve the dismal prognosis of this disease.

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Review

Expert Opinion

Pharmacotherapy of chronic hepatitis C virus infection – the IDEAL trial: '2b or not 2b (= 2a), that is the question?'

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Background: There has been no direct comparison of the antiviral efficacy and the adverse effects of peginterferon (PEG-IFN) alfa-2a and PEG-IFN alfa-2b when used in combination therapy with ribavirin for chronic hepatitis C virus (HCV) infection. *Objective*: A head-to-head comparison of the antiviral efficacy and the adverse effects of PEG-IFN alfa-2a and PEG-IFN alfa-2b was made based on the results from the IDEAL trial, a large, multicenter, prospective, randomized, controlled study performed in the United States to provide guidance for the selection of the right PEG-IFN in clinical settings. *Methods*: The results of the IDEAL trial were analyzed. *Results/conclusion*: The antiviral efficacy, as well as the adverse effects, of PEG-IFN alfa-2a and PEG-IFN alfa-2b are similar in US patients with HCV genotype 1 when used in a standard dosing regimen in combination with ribavirin.

Keywords: adverse effects, antiviral efficacy, IDEAL trial, peginterferon alfa-2a, peginterferon alfa-2b, ribavirin

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1. Introduction

Since the first report on the efficacy of interferon (IFN) therapy on non-A, non-B chronic hepatitis was published in 1986 [1], many studies have been performed on the efficacy of antiviral therapy with IFN on chronic hepatitis C virus (HCV) infection for the eradication of HCV. Some studies further reported long-term improvement of liver fibrosis in patients with the eradication of HCV [2-7], and other studies reported improvement of liver steatosis [8] or reduction in the incidence of the development of hepatocellular carcinoma [9-15].

Since the establishment of IFN therapy as a treatment of chronic hepatitis C, two important developments have occurred; one is the emergence of ribavirin used in combination with IFN and the other is the pegylation of IFN to create peginterferon (PEG-IFN). These developments have contributed to the increase in the rate of sustained virologic response (SVR, Table 1), which usually indicates the eradication of HCV.

Currently, combination therapy with PEG-IFN and ribavirin is the standard antiviral therapy for chronic hepatitis C [16]. The selection of the specific regimen of the PEG-IFN/ribavirin combination therapy is determined by the patient HCV genotype and the virological response after the start of therapy. Patients infected with HCV genotypes 1 or 4, which are usually resistant to the therapy, are recommended to undergo a 48-week treatment regimen, whereas patients infected with HCV genotypes 2 or 3, which are usually sensitive to the therapy, are recommended to undergo a 24-week treatment regimen [16-21]. Several additional findings have been reported, which contribute to regimen selection. Efficacy of elongation of the treatment

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Table 1. The definition of virologic responses and abbreviations.

Term	Abbreviation	Definition
Rapid virologic response	RVR	Undetectable serum HCV RNA after 4 weeks of treatment
Early virologic response	EVR	Undetectable serum HCV RNA (complete EVR) or > 2-log drop in HCV RNA concentration (partial EVR) after 12 weeks of treatment
Slow virologic response		Undetectable serum HCV RNA between 12 and 24 weeks after start of treatment
End-of-treatment response	EoTR	Undetectable serum HCV RNA at the end of treatment
Sustained virologic response	SVR	Continued undetectable serum HCV RNA 6 months after the end of treatment
Relapse		Detectable serum HCV RNA within 6 months after the end of treatment after EoTR

duration up to 72 weeks was reported in patients with HCV genotype 1 having slow virologic response (Table 1) [22-24], whereas a 48-week treatment regimen is recommended in patients having an early virologic response (EVR, Table 1). By contrast, it has been reported that for patients with HCV genotypes 2 or 3 and having a rapid virologic response (RVR, Table 1), it may be possible to shorten the treatment duration to as short as 12 weeks [25-29]. In addition, multiple studies report the importance of the adherence to the therapy for achieving SVR [30-33].

One question remains unanswered, however. Which PEG-IFN should be administered in combination with ribavirin: PEG-IFN alfa-2a or PEG-IFN alfa-2b? Physicians may wonder, like Hamlet, '2b or not 2b (= 2a), that is the question'.

Recently, a large prospective, randomized, controlled trial (the IDEAL trial) was conducted, in which antiviral efficacy and adverse effects were compared between patients treated with PEG-IFN alfa-2a and those treated with PEG-IFN alfa-2b. The results of this trial may provide some answers to this question. In this review, we compare the pharmacological characteristics, antiviral efficacy, and adverse effects of PEG-IFN alfa-2a and PEG-IFN alfa-2b as seen from the results of the IDEAL trial and other studies. We will discuss our interpretation of the results and strategy of choosing the kind of PEG-IFN for antiviral therapy for chronic hepatitis C.

2. IFN alfa-2a and IFN alfa-2b (monotherapy and combination therapy with ribavirin)

IFN alfa-2a and IFN alfa-2b are recombinant DNA-derived protein products with substantial amino-acid sequence identity to endogenous IFNs. Both are type I alfa IFN. The first IFN treatment regimen for antiviral therapy against HCV was simply IFN monotherapy. Before ribavirin, a synthetic guanosine nucleoside analog came to be used in combination with IFN, many investigators attempted to increase the rate of SVR with IFN monotherapy. The techniques used included increasing the dose of IFN or lengthening either the entire treatment period or the period of daily administration [34-56]. However, the increase was minimal, especially in patients infected with HCV genotype 1. The rate of SVR in patients with HCV genotype 1 was usually < 15% [57-60]. Although no report directly compared the rate of SVR between patients who received IFN alfa-2a monotherapy and those who received IFN alfa-2b monotherapy, the rate of SVR was similar in the two groups [57-60].

The use of ribavirin in combination with IFN alpha significantly increased the rate of SVR [57,58,61], including cases of retreatment [62-65]. The effect of the addition of ribavirin to IFN alfa on the increase in SVR rate was similar between IFN alfa-2a and IFN alfa-2b; however, no report directly compared the rate of SVR between patients who received combination therapy with IFN alfa-2a plus ribavirin and those who received combination therapy with IFN alfa-2b plus ribavirin.

3. PEG-IFN alfa-2a and PEG-IFN alfa-2b

In the late 1990s, PEG-IFN, a pegylated form of IFN alfa, became available for antiviral treatment of patients with chronic hepatitis C. Conjugation of an inert polyethylene glycol (PEG) molecule to a core protein (IFN alfa in this case) is a well-established method of modifying the pharmacological characteristics of the core protein [66-68]. Indeed, IFN alfa and PEG-IFN alfa differ greatly in their pharmacokinetics (Figure 1). This difference results in a higher SVR rate and fewer adverse effects in patients treated with PEG-IFN compared with those treated with IFN alfa, for both alfa-2a and alfa-2b [69-73].

PEG-IFN alfa-2a and PEG-IFN alfa-2b differ in the size and structure of the interferon and polyethylene glycol molecules, as well as in their pharmacokinetic properties [74-79]. The differences in chemical properties and pharmacokinetics are listed in Table 2. PEG-IFN alfa-2a is produced by forming a covalent bond between a branched 40-kDa PEG molecule and the IFN alfa-2a core protein. PEG-IFN alfa-2b is produced by forming a covalent bond between a linear 12-kDa PEG molecule, monomethoxypolyethylene glycol (mPEG), and the IFN alfa-2b core protein (Figure 2). Each PEG-IFN has a different advantage in yielding antiviral efficacy. PEG-IFN alfa-2a has the longer half-life of the two, whereas PEG-IFN alfa-2b has higher specific antiviral activity. The US Food and Drug Administration (FDA)-approved dosing regimen also differs between the two PEG-IFNs: fixed dosing for PEG-IFN alfa-2a and dosing based on weight for PEG-IFN alfa-2b [80,81]. Although it is presumed

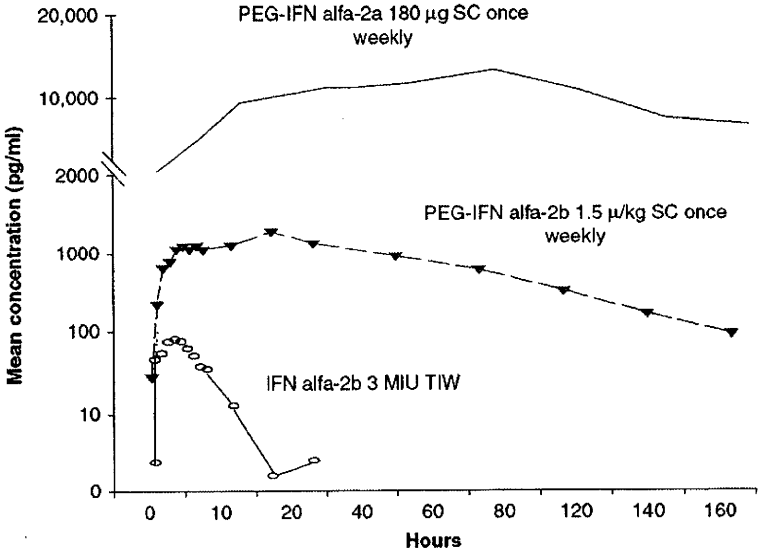

Figure 1. Pharmacokinetics of IFN alfa and PEG-IFN alfa.

that these differences will result in a different antiviral efficacy between the two types of PEG-IFN, no head-to-head results were reported for these two drugs during the period when PEG-IFN monotherapy was the mainstream antiviral therapy for chronic hepatitis C.

4. Previous comparisons of the rate of sustained virologic response between PEG-IFN alfa-2a and PEG-IFN alfa-2b as combination therapy with ribavirin

Combination therapy with PEG-IFN and ribavirin is the current standard antiviral therapy for the treatment of chronic hepatitis C. The use of PEG-IFN in combination with ribavirin has been reported to be superior to combination therapy with standard IFN and ribavirin [82-86], and the addition of ribavirin to PEG-IFN has been reported to be superior to PEG-IFN monotherapy [83,85,87-89]. Many studies have documented a high rate of SVR from combination therapy with PEG-IFN and ribavirin in various patient subpopulations, including patients undergoing the therapy as a retreatment [17-29,90-102].

The ribavirin itself is pharmacologically identical, whether administered in combination with PEG-IFN alfa-2a or PEG-IFN alfa-2b, despite the different names. Therefore, a difference in the antiviral efficacy, if observed, would be due either to the difference between IFN alfa-2a and IFN alfa-2b, the difference in the type of pegylation, or the different dosing regimens or dose reduction rules of PEG-IFN and ribavirin associated with the type of PEG-IFN used. Because similar SVR rates have been observed in patients who received IFN alfa-2a and in those who received IFN alfa-2b, it is presumed that the difference in the type of pegylation and the different dosing regimen would have the strongest impact on the difference in antiviral efficacy. Whether the difference in these factors does in fact cause the observed difference in SVR rate in clinical practice is, therefore, of great interest.

Two earlier studies attempted a direct comparison of antiviral efficacy between PEG-IFN alfa-2a and PEG-IFN alfa-2b in randomized trials [103,104]. However, the number of patients evaluated in these trials was too small (n = 36 and n = 116) and the follow-up period was too short. Furthermore, the trials evaluated heterogeneous interventions and populations. A more recent study focused on patients who were infected with HCV genotype 1 and had a high pretreatment HCV RNA concentration (i.e., difficult-to-treat patients) and reported comparable antiviral efficacy between PEG-IFN alfa-2a plus ribavirin and PEG-IFN alfa-2b plus ribavirin [105]. The authors of this study also reported a higher rate of discontinuation of the therapy due to adverse effects in patients treated by PEG-IFN alfa-2b plus ribavirin. The study contained a fairly large number of patients (n = 380) and was a prospective, randomized trial. The reported observations, however, only extended to 12 weeks after start of treatment, at which time the antiviral efficacy was evaluated by EVR. Although EVR is an established marker of SVR, the final outcome should be evaluated as well. Another study compared the antiviral efficacy of PEG-IFN alfa-2a and PEG-IFN alfa-2b in combination with ribavirin and found a similar rate of SVR between the two groups [106]. Their study was prospective but lacked randomization.

Chou *et al.* [107] attempted an indirect analysis of reported randomized trials to compare the rate of SVR between patients who received PEG-IFN alfa-2a plus ribavirin and those who received PEG-IFN alfa-2b plus ribavirin. They found no statistically significant difference in SVR rate between these

Table 2. Chemical and pharmacokinetic profiles of PEG-IFN alfa-2a and PEG-IFN alfa-2b.

	PEG-IFN alfa-2a	PEG IFN alfa-2b
Size of PEG	40 kDa	12 kDa
Conjugation form	Branched	Linear
Half-life	77 – 100 h	30 – 60 h
Specific activity	7%	28%
Dosing regimen	Fixed dose (180 µg)	Adjustment by weight (1.5 µg/kg)

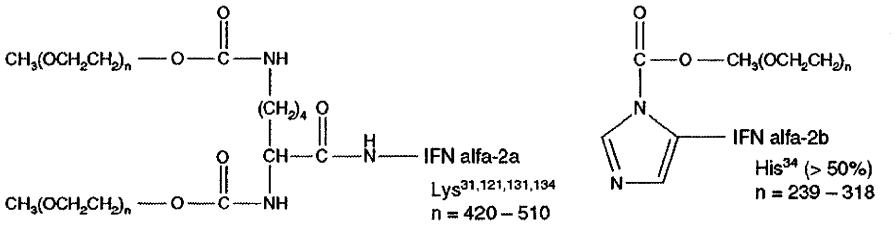

Figure 2. Chemical structures of PEG-IFN alfa-2a and PEG-IFN alfa-2b.

two groups. When only patients with HCV genotype 1 were considered, there was still no difference. Despite these studies, it is clear that a large, well-designed prospective trial is necessary to reach a conclusion on the difference in antiviral efficacy and adverse effects between PEG-IFN alfa-2a plus ribavirin and PEG-IFN alfa-2b plus ribavirin.

5. The IDEAL trial

The IDEAL trial (Individualized Dosing Efficacy vs flat dosing to Assess optimaL peginterferon therapy) was a US, multicenter, prospective, randomized, controlled trial with the purpose of head-to-head comparison of PEG-IFN alfa-2a plus ribavirin and PEG-IFN alfa-2b plus ribavirin for antiviral efficacy against chronic HCV infection. The trial contained a sufficiently large number of patients (n = 3070) and focused on patients with HCV genotype 1 [108]. In this trial, enrolled patients were randomly assigned to one of three groups: weekly 1.0 µg/kg PEG-IFN alfa-2b with daily 800 – 1400 mg ribavirin (low-dose PEG-IFN alfa-2b + ribavirin, n = 1016), weekly 1.5 µg/kg PEG-IFN alfa-2b with daily 800 – 1400 mg ribavirin (standard-dose PEG-IFN alfa-2b + ribavirin, n = 1019), and weekly 180 µg PEG-IFN alfa-2a with daily 1000 – 1200 mg ribavirin (PEG-IFN alfa-2a + ribavirin, n = 1035). Patients in all three groups received 48 weeks of treatment, followed by a 24-week follow-up period (Figure 3) [108]. Ribavirin dosages were modified in response to anemia, an adverse effect of ribavirin, as follows: reduction by 200 or 400 mg in the PEG-IFN alfa-2b groups, and to 600 mg in the PEG-IFN alfa-2a group [108]. The comparison between the latter two groups was a head-to-head comparison between PEG-IFN alfa-2a plus ribavirin and PEG-IFN alfa-2b plus ribavirin with the current standard dosage.

The final results of this trial were recently published [109]. The study patients consisted of 3070 treatment-naïve patients from 118 US centers with chronic HCV genotype 1 infection. The baseline demographics of patients were similar across the three groups. For the two head-to-head comparison groups (standard-dose PEG-IFN alfa-2b + ribavirin and PEG-IFN alfa-2a + ribavirin), they were as follows: male, 60.2 and 59.2%; white ethnicity, 71.8 and 70.8%; black ethnicity, 18.0 and 19.3%; mean age, 47.5 years and 47.6 years; mean weight, 84.0 kg and 82.8 kg; high pretreatment HCV RNA concentration (> 600,000 IU/mL), 82.0 and 82.3%; high fibrosis grade (grade 3 or 4 by METAVIR fibrosis score), 10.9 and 10.6%.

The antiviral efficacies for all three groups are listed in Table 3. The rate of end-of-treatment response (EoTR, Table 1) in patients who received PEG-IFN alfa-2a plus ribavirin was higher than in patients who received standard-dose PEG-IFN alfa-2b plus ribavirin (64.4 vs 53.2%, p < 0.0001). In contrast, the relapse rate after completion of the therapy in patients who received standard-dose PEG-IFN alfa-2b plus ribavirin was lower than in patients who received PEG-IFN alfa-2a plus ribavirin (23.5 vs 31.5%, p = 0.0024). As a result, the rate of SVR was similar between the two groups (40.9% for PEG-IFN alfa-2a and 39.8% for PEG-IFN alfa-2b, p = 0.5687). The similarity of the rate of SVR between patients treated with PEG-IFN alfa-2a and ribavirin and those treated with standard-dose PEG-IFN alfa-2b (1.5 µg/kg) was maintained within subgroups: female (41.9 vs 44.3%)/male (40.1 vs 36.9%), black ethnicity (26.0 vs 23.0%)/white ethnicity (44.2

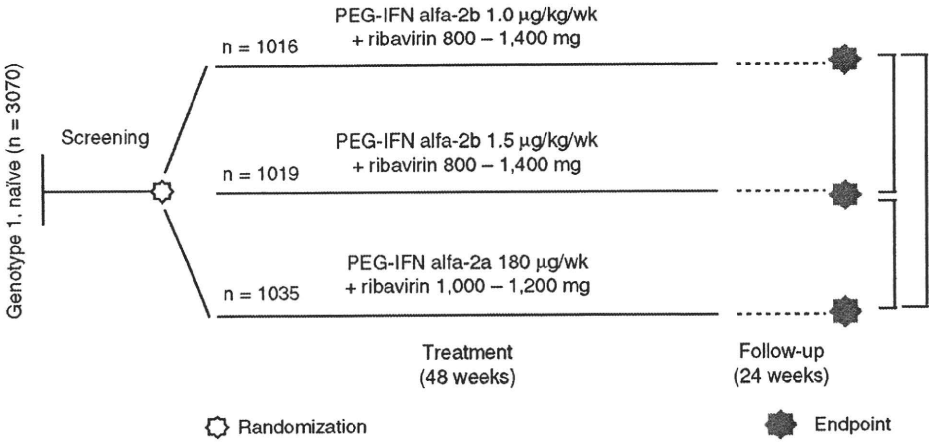

Figure 3. Study design of the IDEAL trial.

Table 3. The rate of rapid virologic response, early virologic response, end-of- treatment response, sustained virologic response, and relapse in three arms of the IDEAL study.

	PEG-IFN alfa-2b 1.0 µg/kg/week + ribavirin 800 – 1400 mg (n = 1016)	PEG-IFN alfa-2b 1.5 µg/kg/week + ribavirin 800 – 1400 mg (n = 1019)	PEG-IFN alfa-2a 180 µg/week + ribavirin 1000 – 1200 mg (n = 1035)
RVR (4 weeks)	7.8%	11.4%	11.9%
EVR (12 weeks)	36.0%	39.9%	45.0%
EoTR (48 weeks)	49.2%	53.2%	64.4%
SVR (24 weeks -up)	38.0%	39.8%	40.9%
lapse rate	20.0%	23.5%	31.5%

vs 43.6%), pretreatment fasting glucose < 5.6 mmol/L (44.1 vs 43.7%)/≥ 5.6 mmol/L (32.9 vs 29.7%), patients without steatosis (49.3 vs 47.6%)/with steatosis (36.4 vs 34.5%), pretreatment HCV RNA concentration > 600,000 IU/mL (35.6 vs 35.3%)/≤ 600,000 IU/mL (65.6 vs 60.7%), and METAVIR fibrosis score 0 to 2 (43.6 vs 42.1%)/3 or 4 (23.6 vs 20.7%). In multivariate analysis, the factors that influenced SVR were low pretreatment HCV RNA concentration (≤ 600,000 IU/mL), non-black ethnicity, minimal fibrosis score (METAVIR 0 to 2), lack of steatosis, pretreatment fasting glucose < 5.6 mmol/L, and pretreatment ALT elevation. The kind of PEG-IFN used (2a or 2b) did not have an impact on SVR.

As with the SVR rate, the rate of adverse effects and the rates of dose modification and discontinuation due to adverse effects were similar between patients treated with PEG-IFN alfa-2a plus ribavirin and those treated with standard-dose PEG-IFN alfa-2b plus ribavirin (Table 4). The percentages of patients who discontinued the therapy due to adverse effects were 13.0 and 12.7%, and the percentage of patients who experienced a dose reduction due to adverse effects were 42.9 and 43.3%, respectively. With regard to hematologic parameters, neutrophil counts fell below 750/mm^3 and 500/mm^3 in 27.0 and 5.9% of patients, respectively, who received PEG-IFN alfa-2a plus ribavirin, and in 22.2 and 2.8% of patients, respectively, who received standard-dose PEG-IFN alfa-2b plus ribavirin. The reduction of neutrophil counts was more marked in patients who received PEG-IFN alpha-2a ($p = 0.01$ and $p = 0.001$, respectively). Hemoglobin level fell below 10 g/dL and 8.5 g/dL in 29.6 and 3.8% of patients, respectively, who received PEG-IFN alfa-2a plus ribavirin, and in 30.7 and 2.5% of patients, respectively, who received standard-dose PEG-IFN alfa-2b plus ribavirin. No difference was found in hemoglobin reduction between the two groups.

6. Other studies comparing PEG-IFN alfa-2a and PEG-IFN alfa-2b in combination with ribavirin

In addition to the IDEAL trial, several other studies have attempted a direct comparison between PEG-IFN alfa-2a and PEG-IFN alfa-2b treatment (Table 5). In a single-center, prospective, randomized, controlled trial conducted in Italy and containing 320 patients including genotypes 1, 2, 3, and 4,

Table 4. The rate of dose modification and discontinuation due to adverse effects in three arms of the IDEAL study.

	PEG-IFN alfa-2b 1.0 μg/kg/week + ribavirin 800 – 1400 mg (n = 1016)	PEG-IFN alfa-2b 1.5 μg/kg/week + ribavirin 800 – 1400 mg (n = 1019)	PEG-IFN alfa-2a 180 μg/week + ribavirin 1000 – 1200 mg (n = 1035)
Dose modification due to adverse effects	33.3%	43.3%	42.9%
Discontinuation due to adverse effects	9.6%	12.7%	13.0%

Table 5. Studies comparing PEG-IFN alfa-2a and PEG-IFN alfa-2b in patients with HCV genotype 1.

Authors (country)	Study name	Method	RCT	No. of sites	No. of cases	Results (SVR rate)	
						PEG 2a	PEG 2b
McHutchison *et al.* (USA)	IDEAL	Prospective	Yes	Multi-center	3070	41%	40%
Ascione *et al.** (Italy)		Prospective	Yes	Single-center	186	55%	40%
Witthoeft *et al.* (Germany)	PRACTICE	Retrospective	No	Multi-center	1128‡	50%	44%
Craxi *et al.* (Italy)	PROBE	Retrospective	No	Multi-center	1351	41%	34%
Rumi *et al.** (Italy)	MIST	Prospective	Yes	Multi- center	222	48%	32%

*Including patients with HCV genotype 4.
‡Matched pair patients.
*All but IDEAL trial were reported as abstracts and have not been published.
PEG 2a: PEG-IFN alfa-2a; PEG 2b: PEG-IFN alfa-2b; RCT: Randomized controlled trial.

Ascione *et al.* [110] reported a higher SVR rate in patients treated by PEG-IFN alfa-2a plus ribavirin than in those treated by PEG-IFN alfa-2b (1.5 μg/kg) plus ribavirin (68.7 vs 54.4%, $p = 0.0082$). A higher SVR rate in patients treated by PEG-IFN alfa-2a plus ribavirin was also observed when only patients with HCV genotype 1 or 4 were considered (54.8 vs 39.8%, $p = 0.0398$). Another prospective study from Italy in which PEG-IFN alfa-2a and PEG-IFN alfa-2b in combination with ribavirin were directly compared (MIST study) reported a higher rate of SVR in patients treated with PEG-IFN alfa-2a plus ribavirin in 431 patients with HCV genotype 1, 2, 3, and 4 (66 vs 54%, $p = 0.02$), and when with HCV genotypes 1 and 4 were considered separately (48 vs 32%, $p = 0.02$) [111]. In the former study, however, the rate of withdrawal of the therapy observed with PEG-IFN alfa-2b plus ribavirin was markedly higher than in patients treated by PEG-IFN alfa-2a plus ribavirin. This is in contrast to the result of the IDEAL trial in the U.S. However, another retrospective study from the US also reported higher treatment persistence in patients treated with PEG-IFN alfa-2a plus ribavirin than in those treated with PEG-IFN alfa-2b plus ribavirin [112]. Further studies will be required on adverse effects and the treatment adherence for the two treatments in different patient populations.

Other reported studies were retrospective, non-randomized comparisons. Two retrospective studies from Italy and from Germany found a higher rate of SVR in real-life settings in patients treated with PEG-IFN alfa-2a plus ribavirin than in those treated with PEG-IFN alfa-2b plus ribavirin [113,114].

Craxi *et al.* [113] studied 1017 naïve patients with HCV genotype 1 who were included in the Italian PROBE study. PEG-IFN alfa-2a and ribavirin were administered to 663 patients, and PEG-IFN alfa-2b and ribavirin to 354 patients. The rate of SVR was 35% for PEG-IFN alfa-2a and 23% for PEG-IFN alfa-2b ($p = 0.01$). The use of PEG-IFN alfa-2a was shown by multivariate analysis to be one of the independent factors accounting for the higher SVR rate.

Witthoeft *et al.* [114] compared the results observed with PEG-IFN alfa-2a and PEG-IFN alfa-2b by matched pair analysis, including cumulative ribavirin dosage, in patients included in the German PRACTICE study. In 1696 patients with all genotypes, the rate of SVR was 59.3% in patients treated with PEG-IFN alfa-2a plus ribavirin and 53.0% in those treated with PEG-IFN alfa-2b plus ribavirin. In 1128 patients with HCV genotype 1, the SVR rates were 50 and 44%, respectively. The SVR rate was significantly higher in the PEG-IFN alfa-2a group both for all genotypes and for the patients with HCV genotype 1 considered separately ($p = 0.008$ and $p = 0.04$, respectively). By contrast, another study from Australia [115] reported a comparable rate of SVR between PEG-IFN alfa-2a and PEG-IFN alfa-2b treatments in patients with HCV genotypes 1, 2, or 3.

Unfortunately, those studies that attempted a direct comparison between PEG-IFN alfa-2a and PEG-IFN alfa-2b have been reported as an abstract form, and final results have not been published. The detailed analyses of the data in these studies that would be published in the future will more clarify

their conclusions. The result of the MIST study will be published in the near future in *Gastroenterology*.

Three studies (one prospective and two retrospective) of patients with HCV and HIV co-infection attempted a direct comparison between PEG-IFN alfa-2a and PEG-IFN alfa-2b in combination with ribavirin [116-118]. All three studies reported no difference in SVR rate between PEG-IFN alpha-2a and PEG-IFN alpha-2b.

7. Conclusion

The differing pharmacokinetics and antiviral activities of PEG-IFN alfa-2a and -2b have long been known. However, whether these differences and the differences in dosing regimen cause differences in treatment outcomes has remained unclear. Data from the IDEAL trial provided one answer to this question. According to the results of this large, prospective, randomized, controlled trial, the final SVR rate and adverse effects of PEG-IFN alfa-2a and PEG-IFN alfa-2b are similar in patients with HCV genotype 1, when used with the standard dosing regimen in combination with ribavirin.

8. Expert opinion

The IDEAL trial showed that the two currently available PEG-IFNs – PEG-IFN alfa-2a and PEG-IFN alfa-2b – in combination with ribavirin, are comparably effective against chronic HCV genotype 1 infection, despite their differing chemical and pharmacokinetic profiles. The IDEAL study protocol was well-designed and contained a sufficiently large number of patients, making it fairly reliable. Although each PEG-IFN has advantages, revealed by detailed analysis, the overall antiviral efficacy appears to be similar from the aspect of the eradication of HCV. The choice of PEG-IFN has weak influence on the SVR rate, in comparison to other factors such as treatment duration or adherence.

Of course, different study populations with differing background characteristics may give different results. The IDEAL trial contained only US patients; the background characteristics of patients in other studies will not be the same. Indeed, four other studies from Italy and Germany reported a result that contradicts the IDEAL study: a higher SVR rate in patients treated with PEG-IFN alfa-2a plus ribavirin than in those treated with PEG-IFN alfa-2b plus ribavirin; however, two of these studies were retrospective and the other two were based on a smaller number of patients than the IDEAL trial. In addition, data were lacking on a direct comparison between PEG-IFN alfa-2a plus ribavirin and PEG-IFN alfa-2b plus ribavirin in Asian patients. Further studies are necessary on this issue in various patient populations. Also, the different dosing regimen and the different dose reduction rules of PEG-IFN and ribavirin may give different results. The dosing regimen and dose reduction rules in the IDEAL trial were based on those approved by the US FDA, and would be different in other countries. The dosing regimen and dose reduction rules in the IDEAL trial were different between PEG-IFN alfa-2a plus ribavirin and PEG-IFN alfa-2b plus ribavirin. The direct comparison between PEG-IFN alfa-2a and PEG-IFN alfa-2b treatment using the same dosing regimen and same dose reduction rules will be necessary for more accurate comparison of antiviral efficacy between these two PEG-IFNs.

Despite these issues, it appears that, to the question posed at the introduction of this review, we can answer '2b or not 2b (= 2a), we can select either one', for initial treatment of a naïve patient with chronic HCV genotype 1 infection. In this situation, physicians may select either kind of PEG-IFN in combination with ribavirin. They may, therefore, select alfa-2a or alfa-2b according to the patient's social factors including availability and cost.

As many practical clinicians treating individual patients have experienced, however, the fact that a patient did not achieve SVR with one PEG-IFN does not necessarily mean that the patient will have no chance to achieve SVR with the other. Despite the similar rate of SVR between patients treated with PEG-IFN alfa-2a and PEG-IFN alfa-2b, their efficacies can be different for individual patients. Many hepatologists have seen cases in which a patient who had failed to achieve SVR with PEG-IFN alfa-2a plus ribavirin experienced successful eradication of HCV with PEG-IFN alfa-2b plus ribavirin, and vice versa. Although the final SVR rates were similar between PEG-IFN alfa-2a plus ribavirin and PEG-IFN alfa-2b plus ribavirin in the IDEAL trial, the EoTR rate and relapse rate were significantly different. These results suggested the different antiviral efficacy between these two PEG-IFNs, despite similar final SVR rates. It is, therefore, not completely futile to attempt to retreat patients who failed to achieve SVR by one PEG-IFN plus ribavirin with the other PEG-IFN plus ribavirin. Several studies, notably the REPEAT and EPIC3 studies [119-121] reported on the data of retreatment of patients who failed to achieve SVR by previous combination therapy with PEG-IFN and ribavirin. Although the SVR rate was low in both studies, the former study contained patients with genotype 1 who failed to achieve SVR with PEG-IFN alfa-2b plus ribavirin, but achieved SVR with PEG-IFN alfa-2a plus ribavirin. Conversely, the latter study contained patients with genotype 1 who failed to achieve SVR with PEG-IFN alfa-2a plus ribavirin, but achieved SVR with PEG-IFN alfa-2b plus ribavirin. However, as the guidelines of the American Association for the Study of Liver Diseases (AASLD) do not recommend retreatment for patients who failed to achieve SVR by PEG-IFN alfa plus ribavirin for the purpose of eradication of HCV [16], the retreatment should be considered for limited cases who cannot wait for the clinical use of new antiviral agents against HCV or who cannot apply for these drugs. In addition, the consideration of retreatment with PEG-IFN plus ribavirin is only for patients who have relapsed; patients who showed no response to one PEG-IFN plus ribavirin should not be retreated with the other PEG-IFN plus ribavirin.

More importantly, the adverse effects of PEG-IFN alfa-2a and PEG-IFN alfa-2b differ between individual patients, although the rates of adverse effects are similar between the

two treatments. In the IDEAL trial, the overall rate of common adverse events was similar between patients treated by PEG-IFN alfa-2a plus ribavirin and those treated by standard-dose PEG-IFN alfa-2b plus ribavirin, but the details of adverse events were heterogenous. The severity of adverse events from PEG-IFN alfa-2a and PEG-IFN alfa-2b can also vary among individuals. Some patients who discontinue the treatment regimen because of adverse effects from one PEG-IFN might have completed the entire treatment regimen with the other, thereby achieving SVR. In consideration of this, the PEG-IFN type should be selected not on the basis of efficacy but rather on the basis of adverse effects, so as to maintain the adherence that is strongly associated with the likelihood of SVR.

In light of these results, switching the PEG-IFN type during the treatment period may be a possible option. Early prediction of the eventual response to the therapy during the treatment will, therefore, become more important. Specifically, early prediction of a lack of SVR will make it possible to switch from PEG-IFN alfa-2a to PEG-IFN alfa-2b, or vice versa, during the course of the treatment. Prediction of the treatment outcome on the basis of RVR or EVR has been reported. This information, as well as the appearance and severity of adverse effects, could determine whether to switch the PEG-IFN type during the early stage of treatment, reducing unnecessary adverse effects and medical cost and maintaining the adherence.

In addition, it will be important to elucidate patient baseline characteristics to determine which patients should be treated initially with PEG-IFN alfa-2a plus ribavirin and which should be treated initially with PEG-IFN alfa-2b plus ribavirin. PEG-IFN alfa-2a and PEG-IFN alfa-2b are, of course, different drugs and their relative suitabilities for individual patients would be expected to differ. It is undoubtedly better for a patient with chronic hepatitis C to achieve SVR with the initial treatment rather than a retreatment and without switching the type of PEG-IFN during treatment.

Finally, the difference in antiviral efficacy between PEG-IFN alfa-2a and PEG-IFN alfa-2b should be evaluated in the future when used in combination with emerging new drugs, such as HCV serine protease or polymerase inhibitors [122-130], which can enhance the treatment efficacy of PEG-IFN. Although the SVR rates were comparable between PEG-IFN alfa-2a and PEG-IFN alfa-2b in combination with ribavirin, the difference in efficacy between the two PEG-IFNs when used in combination with these new drugs has not been determined.

Declaration of interest

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特集II 肝細胞癌治療後の抗ウイルス療法は予後を改善するか

B型肝炎ウイルス陽性肝細胞癌の治療後の核酸アナログ投与*

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Key Words : hepatitis B, hepatocellular carcinoma (HCC), nucleoside analogues, nucleotide analogues, recurrence

はじめに

ウイルス性肝炎の治療の進歩は目覚しいものがある．とくにB型肝炎ウイルス(hepatitis B virus：HBV)に対する抗ウイルス療法は各種核酸アナログの登場により新たな展開を示している[1]．B型慢性肝炎の治療目標は肝硬変への進展，および発癌を抑制することである．HBV量が増加するに従って肝硬変，肝細胞癌への進展率が増加し，核酸アナログ製剤を使用することにより，これらの進展を抑制できることは，すでに台湾のデータより報告された[2-4]．肝細胞癌が発生する前の肝炎，肝硬変においては，核酸アナログによるウイルス量の抑制が発癌を抑制することが示されているが[5]，肝細胞癌治療後の核酸アナログの適応については，まだコンセンサスが得られていないのが現状である．本稿では，B型慢性肝炎を背景とした肝細胞癌の根治治療後症例において，核酸アナログの肝細胞癌の再発抑制効果，肝予備能の改善効果について検討しデータを示す．

対象と方法

対象は，1989～2007年に当院で経験したHBV陽性肝細胞癌232例中，肝切除もしくは局所治療を受け，局所がコントロールされたと判断され，HBVのマーカーが経時的に測定されていた76例であり，これらをretrospectiveに解析した．平均年齢は59歳(21～84歳)，男女比は62：14，核酸アナログ投与例は31例，非投与例は45例で，観察期間中央値は4.5年(0.9～17.3年)である．生存率の解析はKaplan-Meier法，差の解析はBreslow-Gehan-Wilcoxon検定，多変量解析はCoxの比例ハザードモデル(変数増加法)を用いた．また2群間の比較は，連続変数に関してはt検定，Mann-Whitney U検定を，名義変数はχ^2検定を用いた．血液生化学データの項目で変動の多いALT, AST, γ-GTP, ALP, LDH, AFPはわれわれが以前から提唱している積分平均値を使用した[5]．それ以外の項目は経過観察開始時のものを使用した．

核酸アナログ投与例と非投与例の背景因子は表1に示すとおりであるが，差を認めるのは観察開始時のHBV DNA量であり，核酸アナログ投与例のほうが有意に高い値を示している．核酸アナログの投与基準は各主治医の判断に任せ，

* Nucleot(s)ide analogues lowers tumor recurrence rate after initial treatment for hepatitis B virus-related hepatocellular carcinoma.

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表1　核酸アナログ投与群と非投与群の背景因子

	核酸アナログ非投与群 (n=45)	核酸アナログ投与群 (n=31)	P
年齢（歳）	59(21-84)	56(36-81)	N.S.
性（女/男）	11/34	3/28	N.S.
HBe抗原（陽性/陰性）	6/39	6/25	N.S.
HBV DNA (log copies/ml)	4.9(2.6-8.5)	6.4(2.6-8.4)	0.0174
血小板（$\times 10^4$/mm^3）	12.7(2.2-44.9)	13.9(6.9-24.7)	N.S.
Genotype (B/C)	0/20	1/25	N.S.
Child分類 (A/B/C)	38/5/2	29/2/0	N.S.
AFP (ng/ml)	11(0.8-2467.3)	8.7(2.3-1195)	N.S.
AFP-L3 (%)	0.5(0.0-27.4)	0.5(0.0-61.7)	N.S.
Stage (I/II/III/IV)	20/22/3/0	21/8/2/0	N.S.
初回治療（肝切除/局所治療）	28/17	22/7	N.S.

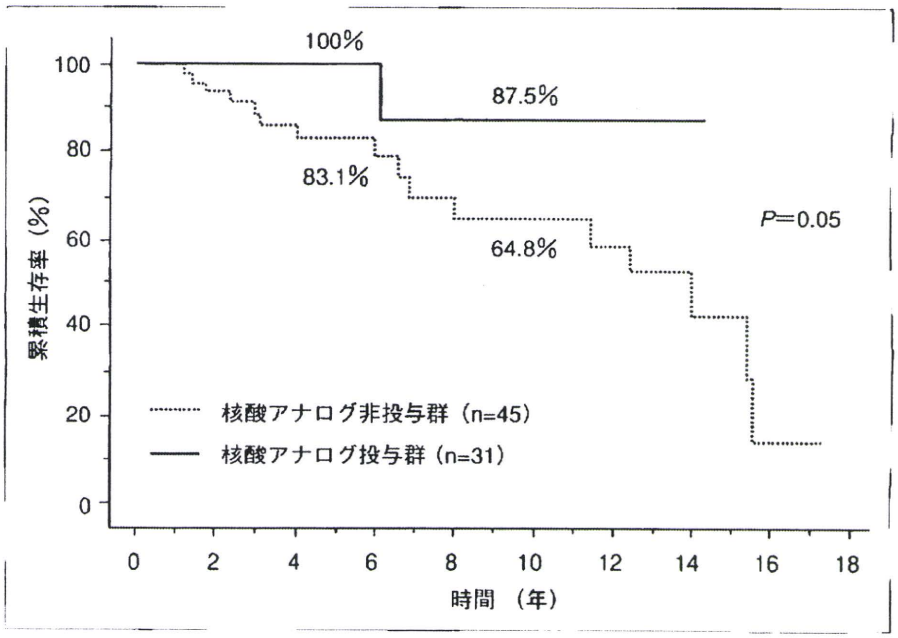

図1　核酸アナログ投与群と非投与群の累積生存率

HBV DNA量の高い症例に投与されたため，核酸アナログ投与例でHBV DNA量が高値となったと考えられる．その他，両者の年齢，性，HBe抗原の有無，血小板，Child分類，stage，初回治療の方法に統計上有意の差を示していない．初回治療の内訳は，54例が肝切除，8例がラジオ波焼灼療法(RFA)，4例が経皮的エタノール注入療法(PEIT)，3例が肝動脈化学塞栓療法(TACE)＋PEIT，5例がTACE＋RFA，1例がTACE＋肝切除，3例がTACEのみであった．なお，肝切除はすべて同じ執刀医である．すべてVpは0で肝外転移は認めなかった．

核酸アナログの内訳は，ラミブジン14名，エンテカビル9名(2名はラミブジンからの変更)，アデフォビル＋ラミブジンが8名であり，全例break through hepatitisを認めていない．

結　果

全体の生存率では核酸アナログ投与群と非投与群で統計上有意の差を認めないまでも5年生存率，10年生存率はそれぞれ100%と83.1%，87.5%と64.8%と投与群で良好であった($P=0.05$)(図1)．全体の累積再発率では5年再発率，10年再発率はそれぞれ25.9%であり，有意の差を認めなかった(図2)．そこでわれわれは，背景因子として有意差の出たHBV DNA量をそろえるた

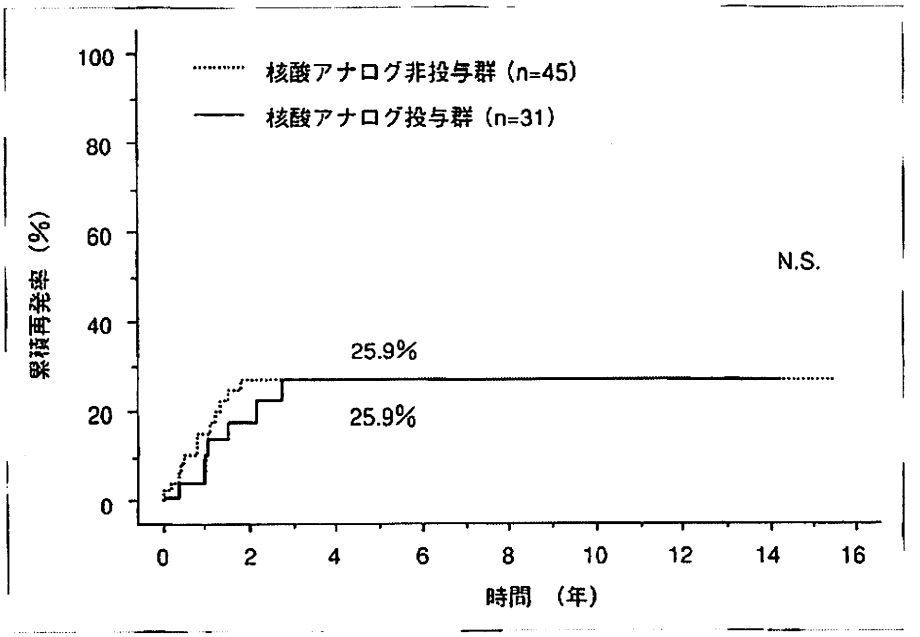

図2 核酸アナログ投与群と非投与群の累積再発率

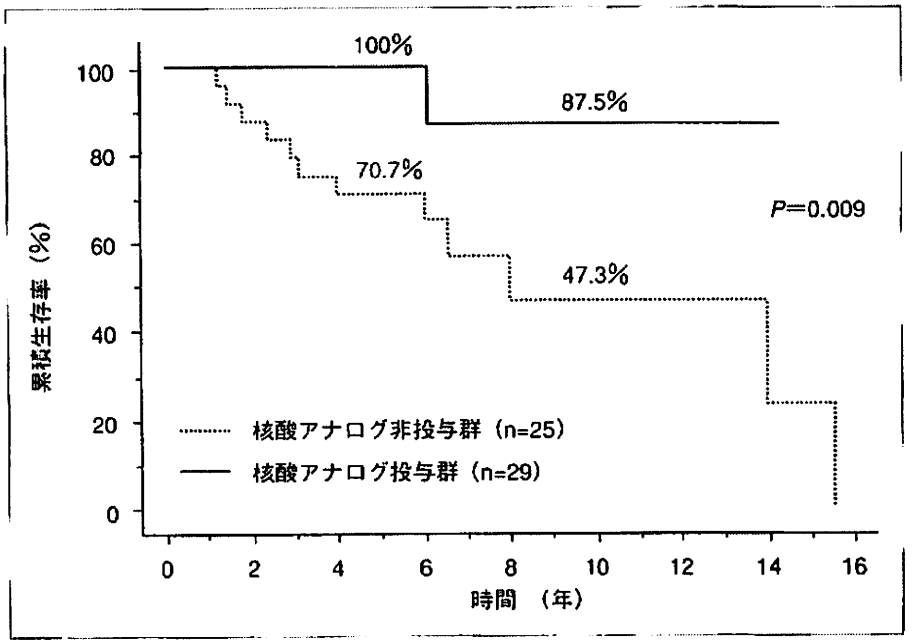

図3 HBV DNA 4 log copies/ml 以上の症例での核酸アナログ投与群と非投与群の累積生存率

めに対象をHBV DNA量が4.0 log copies/ml以上の症例に限定して再度検討を行なった．核酸アナログ投与例が29例，非投与例が25例となり核酸アナログ投与群と非投与群の累積生存率は5年，10年でそれぞれ100%と70.7%，87.5%と47.3%で統計上有意な差を認めた(P=0.009)(図3)．また，累積再発率は5年，10年再発率はそれぞれ56%と45%，56%と45%で統計上有意な差を認めた(P=0.04)(図4)．また，核酸アナログ投与例，非投与例での投与前後の血清総ビリルビン値，アルブミン値の検討をすると，総ビリルビン値では変化を認めなかったが(図5)，アルブミン値では投与群において有意に改善を示した(図6)．

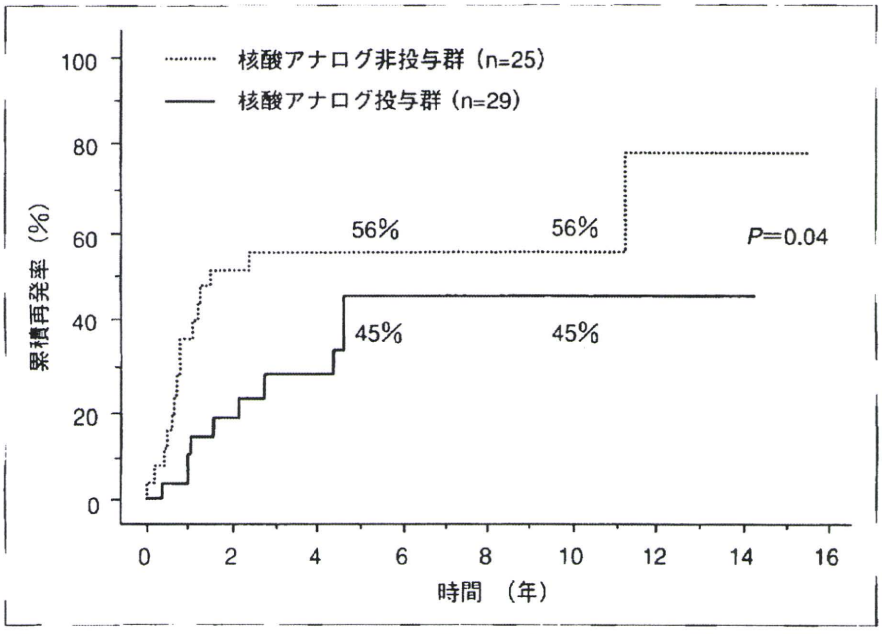

図4　HBV DNA 4 log copies/ml 以上の症例での核酸アナログ投与群と非投与群の累積再発率

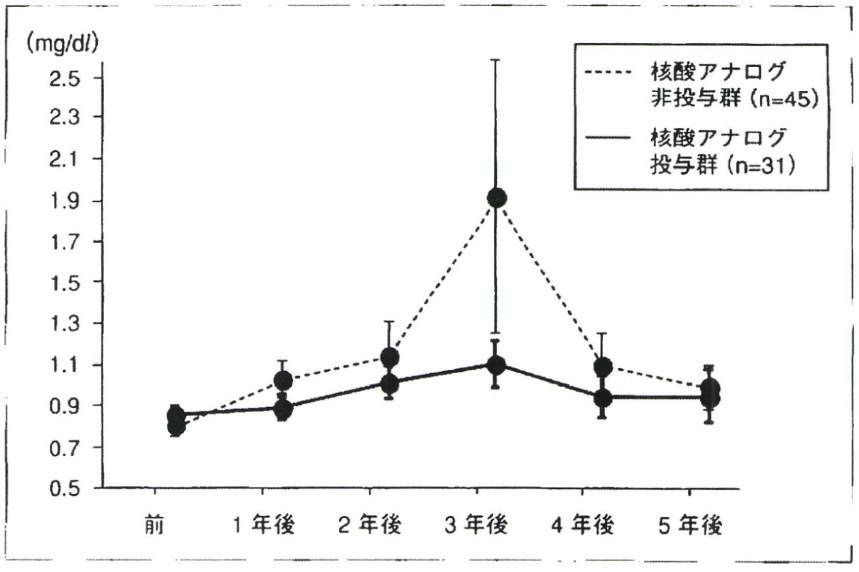

図5　治療前後の総ビリルビン値の変動

考　察

肝細胞癌は手術的に根治を得ても，術後5年で70%の症例が再発するとされている[6]．わが国における肝細胞癌は，B型肝炎ウイルスやC型肝炎ウイルスによる慢性肝障害例に発癌することが多いため，背景肝の改善が肝細胞癌の抑制につながると考えられる．現在，肝細胞癌治療後の再発の予防として多くの治療法が検討されているが，その中で無作為比較試験により有効性が証明されたのはインターフェロン，非環式レチノイド，養子免疫療法のみである[7]．核酸アナログについてはいまだ無作為比較試験により有効性が証明されていない．しかし，肝細胞癌治療後の核酸アナログの投与の報告は，論文で散見される．香港のHungら[8]は72例のHBV陽性肝細胞癌の肝切除術後の患者の再発のリスクは多変量解析で，HBV DNA>4 log copies/ml，AFP

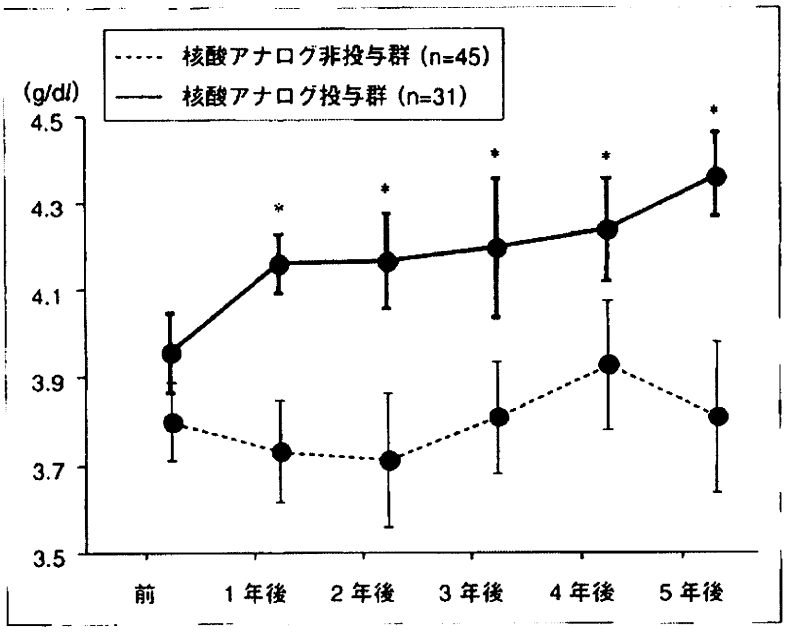

図6 治療前後のアルブミン値の変動
* $P<0.05$

＞1,000ng/ml，腫瘍径＞5 cm，年齢＞60歳であり，その中で，核酸アナログによるHBV DNAを4 log copies/ml未満に抑制している患者は再発が有意に少なかったと報告している．また，Kuzuyaら[9]は，ラミブジン投与群における肝細胞癌の累積再発率は12，24，36か月でそれぞれ13.5%，35.1%，35.1%でありコントロール群の13.4%，39.2%，53.2%と比較し有意な差を認めなかったがラミブジン群で肝機能の改善を認め再発時の治療の選択肢が増えると報告している．Kimらの報告[10]でも核酸アナログ投与により肝機能の改善が認められている．いずれの報告も症例数，観察期間が限定されているが核酸アナログの投与により肝細胞癌の術後の予後の改善が示唆された．当院の検討でも，核酸アナログ投与群で統計上有意とはならないものの生存率で良好な結果を得ており，HBV DNAを4 log copies/ml以上の症例に限ると核酸アナログ投与群で再発率，生存率ともに良好な結果を得ており，また肝機能の改善が認められた．

まとめ

B型肝炎関連の肝細胞癌の根治術後に核酸アナログを投与した群と，非投与群に分けて，累積生存率，累積再発率，肝予備能について検討した．HBV DNAが4.0 log copies/ml以上の症例に限ると投与群で有意に累積生存率，累積再発率で良い結果を認めた．また，肝予備能においても投与群でアルブミン値の上昇を認め改善傾向があった．

以上の結果より，肝細胞癌の根治術後の症例で核酸アナログを投与することにより予後を改善することが示唆された．

なお，本論文要旨は2008年10月に第16回日本消化器関連学会において発表したものである．

文　献

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