34%. Of the 32 cases who were scheduled to receive MCC vaccine by the time of disease onset, only two had been vaccinated more than 10 days before onset; one case developed disease 3 days after vaccination and the remainder were unvaccinated. Each of the 32 cases had an average of 136 children in the cohort matched by date of birth; coverage estimates varied from 1% for cases with onset in mid-January to 65% for cases in mid-July. For cases after this date, the coverage was estimated by projecting towards the national level at the end of August (73%). Use of the individual coverage estimates for each case gave an efficacy of 92% (65–98).

The reduction in serogroup C disease in adolescents is consistent with high vaccine coverage and with high short-term efficacy. In toddlers, the impact was lower, but since vaccinations were still being scheduled during this period, the decline is still consistent with high efficacy. Efficacy data are not yet available for infants, who were scheduled to receive two or three doses; however, disease rates in this age-group have fallen substantially (figure). These results confirm that conjugate vaccines are effective in children younger than two years of age who would not have been protected by plain C polysaccharide vaccines.[1] In line with prelicensing safety studies,[2] suspected reactions to MCC vaccine reported to the Committee on Safety of Medicines have been at a low rate, in line with those of other routine childhood vaccines.[5] Increased surveillance will be maintained to monitor the medium-term and long-term protection from conjugate vaccination to determine whether booster vaccination is necessary.

Serogroup B disease has increased, particularly in the first half of 2000. Disease-causing isolates are being monitored to detect evidence of possible capsule switching as a result of selection pressure by vaccine on serogroup C strains. To date, there has been no evidence of this possibility occurring. Serogroup C disease in older age-groups not scheduled for vaccination has increased by a similar proportion (figure). The increased disease activity caused by other serogroups and in unimmunised age-groups highlights the timeliness of this important public-health intervention and emphasises the need for development of effective vaccines against other serogroups.

We thank Steve Gray, Richard Mallard, Claire Ward, and Usha Gungabissoon for doing the follow-up of the patients, and Marie Rush and Pauline Kaye for collating the coverage data. We also thank all the microbiologists, hospital clinicians, general practitioners, consultants in communicable disease control, district immunisation co-ordinators, and child-health staff for providing additional information on patients.

The Public Health Laboratory Service Meningococcal Reference Unit received support for follow-up of cases from Wyeth Lederle.

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Prevention of hepatocellular carcinoma in patients with chronic active hepatitis C and cirrhosis

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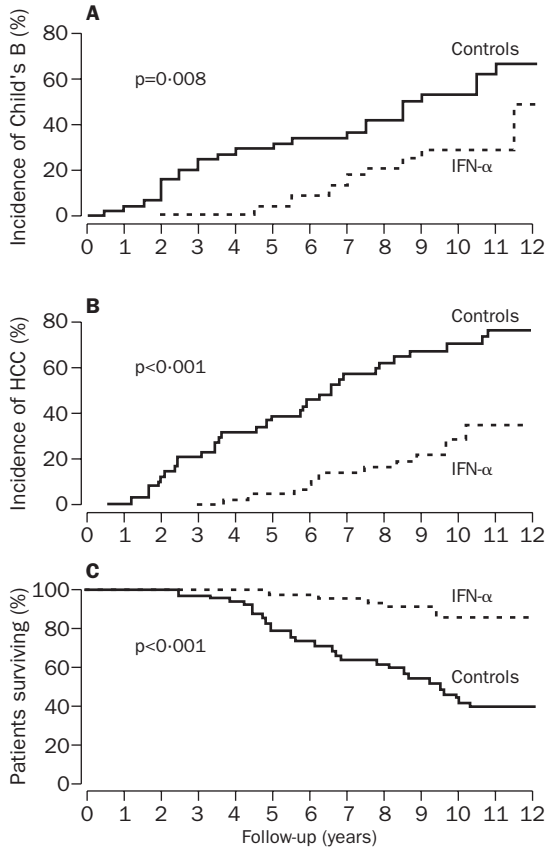
In a prospective randomised controlled study, 90 patients with chronic active hepatitis C and compensated cirrhosis were assigned symptomatic treatment or interferon alfa (IFN-α). We report data on decompensation, detection of hepatocellular carcinoma, and mortality rates. IFN-α gave a sustained response in only a small proportion of patients, but worsening of compensated cirrhosis was prevented and development of hepatocellular carcinoma was inhibited, increasing the survival rate. The risk ratio of IFN-α versus symptomatic treatment decreased by 0·250 for progression to Child-Pugh grade B, 0·256 for detection of hepatocellular carcinoma, and 0·135 for a fatal outcome.

In 1995, we reported that IFN-α prevents hepatocellular carcinoma in some patients with chronic active hepatitis C and cirrhosis in a randomised controlled study after a mean follow-up of 4·9 (SD 1·4) years.[1] We now report clinical results after 8·7 (2·3) years. The protocol of this study was described earlier.[1] 90 patients with chronic active hepatitis C and compensated cirrhosis were selected. The patients were assigned randomly to symptomatic treatment or treatment with IFN-α to start between January, 1988, and June, 1992. The 45 controls received symptomatic therapy and the other 45 patients received 6 MIU of IFN-α (Sumiferon, Sumitomo Pharmaceuticals, Osaka, Japan) three times a week for 24 weeks. The trial accorded with the Helsinki Declaration and was approved by our ethics committee. Statistical analysis was done with SAS software (version 6.12). The χ^2 test was used to assess the homogeneity of groups. Cumulative incidences were plotted by the Kaplan-Meier method, and the statistical significance of differences was examined by the log-rank test. Cox's regression analysis was used for univariate and multivariate analysis. Risk ratios were calculated with the variables of age, α-fetoprotein, alanine aminotransferase (ALT), platelet count, serum albumin, sex, and treatment. Differences with a p value less than 0·05 were taken to be statistically significant.

Maximum, minimum, and mean follow-ups were 11·8, 2·6, and 8·2 (SD 2·7) years, respectively, for controls, and 12·0, 4·4, and 9·2 (1·7) years for patients given IFN-α. The two groups were well balanced for the major prognostic factors of chronic hepatitis C and cirrhosis. During follow-up, 25 (56%) of the controls and 13 (29%) of the patients given IFN-α were rated grade B or worse (p=0·018). IFN-α decreased the cumulative incidence of worsening of the Child-Pugh score (figure). Hepatocellular carcinoma was detected in 33 (73%) of the 45 controls and 12 (27%) of the 45 patients given IFN-α (p<0·001); the cumulative proportion of patients was lower in the group given IFN-α. For patients with mean ALT ⩾80 IU during this trial, these numbers were 23 (79%) of 29 controls and 10 (33%) of 30 patients given IFN-α (p=0·033). 26 (58%) of the controls and 5 (11%) patients in the IFN-α group died during follow-up (p<0·001); the cumulative proportion of overall survival was higher in the group given IFN-α. By univariate analysis, the risk ratios of IFN-α versus symptomatic treatment were 0·302 (95% CI 0·156–0·583) for progression to Child-Pugh B, 0·244 (0·126–0·475) for development of hepatocellular carcinoma, and 0·169 (0·065–0·440) for death, respectively. By multivariate analysis, the risk ratios of treatment were 0·250 (0·124–0·505) for progression to Child-Pugh B, 0·256



Kaplan-Meier estimated probability of decompensation (A) progression to Child-Pugh grade B; (B) hepatocellular carcinoma; and (C) overall survival rate

Variable	Coefficient (β)	Standard error	Wald χ^2	p	Risk ratio (95% CI)
Decompensation					
Age	0·000	0·023	0·000	0·983	1·000 (0·956 to 1·047)
Sex	0·041	0·322	0·016	0·900	1·041 (0·555 to 1·956)
IFN	−1·387	0·359	14·896	<0·001	0·250 (0·124 to 0·505)
Albumin	−1·284	0·436	8·664	0·003	0·277 (0·118 to 0·651)
ALT	−0·002	0·003	0·329	0·566	0·998 (0·990 to 1·005)
Platelet	−0·064	0·048	1·757	0·185	0·938 (0·853 to 1·031)
LogAFP	0·043	0·350	0·015	0·901	1·044 (0·526 to 2·073)
Hepatocellular carcinoma					
Age	0·023	0·025	0·840	0·359	1·023 (0·974 to 1·075)
Sex	0·200	0·317	0·399	0·527	0·818 (0·440 to 1·523)
IFN	−1·364	0·364	14·026	<0·001	0·256 (0·125 to 0·522)
Albumin	−0·643	0·407	2·498	0·114	0·526 (0·237 to 1·167)
ALT	−0·002	0·004	0·286	0·593	0·998 (0·990 to 1·006)
Platelet	−0·041	0·049	0·696	0·404	0·960 (0·871 to 1·057)
LogAFP	0·330	0·363	0·826	0·363	1·391 (0·683 to 2·831)
Overall survival rate					
Age	0·013	0·027	0·236	0·627	1·013 (0·961 to 1·069)
Sex	−0·932	0·413	5·092	0·024	0·394 (0·175 to 0·885)
IFN	−2·003	0·518	14·970	<0·001	0·135 (0·049 to 0·372)
Albumin	−1·131	0·478	5·603	0·018	0·323 (0·127 to 0·823)
ALT	0·000	0·005	0·002	0·963	1·000 (0·990 to 1·011)
Platelet	−0·098	0·061	2·599	0·107	0·906 (0·804 to 1·021)
LogAFP	−0·619	0·462	1·793	0·181	0·539 (0·218 to 1·332)

ALT=alanine aminotransferase.
AFP=αfetoprotein

Risk ratio by variables in Cox regression analysis (multivariate)

(0·125–0·522) for development of hepatocellular carcinoma, and 0·135 (0·049–0·372) for death, respectively (table).

The effects of IFN-α on liver function, hepatocarcinogenesis, and survival rate are still controversial. The disagreement seems to be related to the annual rate of hepatocarcinogenesis in patients with type C cirrhosis being much greater in Japan than in the USA;[2] in countries with low rates, much larger groups of patients are needed for the same statistical power. A second possible explanation is the difference in the patients' backgrounds: factors in addition to hepatitis C virus (HCV) infection (eg, occult hepatitis B virus [HBV] infection[3]) and predisposing characteristics involving race or life-style (such as alcohol intake). Japan has a high rate of HBV carriers; occult HBV infection in patients with type C cirrhosis may contribute to their high rate of hepatocarcinogenesis. A third explanation may be the different treatments used. By contrast with common practice in the western world, all of our patients with large oesophageal varices are treated prophylactically by endoscopic ligation or sclerotherapy (or both), before any rupture.

The longer follow-up makes it possible now to assess the effects of IFN-α on the progress of cirrhosis more accurately. In our first report,[1] the relative risk of hepatocarcinogenesis was 0·067 with IFN-α, but in this update, the risk was 0·256, in agreement with a large-scale retrospective study from Italy.[4] IFN-α given to patients with chronic hepatitis C reduces the relative risk for hepatocarcinogenesis to 0·910 when ALT is substantially increased, 0·358 in those with mildly increased ALT, and 0·197 when it is in the reference range.[5] Hepatocellular carcinoma was detected in only two (13%, 2–40%) of our 15 patients with a complete response to IFN-α (HCV RNA disappeared) or partial response (mean ALT <80 IU); the relative risk was 0·12 (0·03–0·48). In ten (33%, 17%–53%) of the 30 patients who did not respond to IFN-α (ALT remained ⩾80 IU), carcinoma was detected; the proportion was smaller than for the controls (23 [79%] of 29 patients; p=0·033), but inhibition of carcinogenesis by IFN-α was weak. Some part of such inhibition by IFN-α seems to involve its lessening of hepatic inflammation.

Of the 31 control and IFN-treated patients who have died, all but two (94%) died of liver-related causes (27 died of hepatocellular carcinoma). Of the 12 control patients in whom hepatocellular carcinoma has not been detected, nine (75%) are alive, as are all 33 such patients in the IFN-α group.

We thank H Kinoshita, Y Hirota, and S Otani for valuable suggestions; and C Latta for reading the paper. We are grateful to the participants in the trial and to others who contributed but are not named here. We thank E Fukuda for technical assistance, K Nukui for statistical analysis, S Yamamoto, and T Monna. We were supported in part by a grant from the Ministry of Health and Welfare, Japan

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