Hepatitis C viral load testing

March 2000

MSAC application 1021

Assessment report

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The Medicare Services Advisory Committee is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Aged Care on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform Government decisions about which new medical services should attract funding under Medicare.

The hepatitis C viral load testing supporting committee would like to acknowledge the contribution of Dr William Sievert of the Monash Medical Centre.

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MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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Executive summary

The procedure

The tests considered in this report are polymerase chain reaction (PCR)-based tests used in the diagnosis and management of hepatitis C infection. These tests are sophisticated molecular techniques which can detect the ribonucleic acid (RNA) of the virus in a patient's blood. PCR-based techniques can be used in one of three ways:

- to detect if hepatitis C virus is present in a patient's blood;
- to detect the level of HCV RNA viral load; and
- to determine the type of hepatitis C virus present.

The use of PCR-based forms of testing help to decide whether or not to use interferon therapy and to evaluate the response to interferon treatment of hepatitis C.

Medicare Services Advisory Committee – role and approach

The Medicare Services Advisory Committee (MSAC) is a key element of a measure taken by the Commonwealth Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Aged Care on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision making when funding is sought under Medicare. A team from the Australasian Cochrane Centre was engaged to conduct a systematic review of literature on the effectiveness of nucleic acid amplification diagnostic tests for monitoring interferon therapy in patients with chronic hepatitis C. A supporting committee with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of genotyping, and qualitative and quantitative PCR for monitoring interferon therapy in patients with chronic hepatitis C

Clinical need

Hepatitis C is a major public health issue in Australia which results in significant clinical morbidity. The cost of treatment of the disease is expensive, as is the cost of the complications of untreated disease. Evidence now available shows the best therapy for hepatitis C is the combination of interferon and ribavirin. In Australia, Ribavirin is available at present for patients who have failed on interferon monotherapy. In some overseas centres, due to low sustained response rates, interferon monotherapy is now only considered for those patients with a contraindication to ribavirin. A sustained virological response to treatment occurs on average in 40 percent of new patients

although the range of response varies from 30 to 65 percent depending on host and viral factors. Combination therapy is associated with significant adverse events and thus should be considered only for those patients most likely to achieve a long-term benefit.

PCR-based testing has been proposed as a way of enabling both clinicians and patients to have greater certainty regarding treatment decisions for hepatitis C.

Safety

The serological tests considered in this review have only minimal issues of safety.

Effectiveness

Genotyping and viral load testing are predictive of the response to interferon therapy. For any individual patient, however, the predictive value of these tests is not high enough to be used as a means of excluding a patient from treatment on the basis of the results of such testing. Even in patients with a high viral load or a specific genotype, a proportion will respond to interferon therapy, and should be allowed an empirical trial of this form of treatment. Detection of viraemia during the course of interferon therapy has a higher predictive value than pretreatment determinations, and may be used to guide decisions regarding the continuation of therapy.

Cost effectiveness

The cost of the tests is relatively high and the potential number of patients who could be eligible for testing is also high. A simple evaluation of the costs and consequences of testing has demonstrated, however, that with careful patient selection quantitative viral load testing and genotyping may still be the most cost-effective approach.

Recommendation

MSAC recommended that on the strength of evidence pertaining to Hepatitis C Viral Load Testing (MSAC Application 1021) public funding should be supported for these procedures providing the use of these tests is restricted to the consultant physicians who will manage the treatment and is only used for patients with confirmed hepatitis C (by ELISA or PCR test) who undertake antiviral therapy.

MSAC further recommended that:

- genotype testing be restricted to once only for each patient;
- viral load testing be used prior to treatment, and be restricted to once only in any 12-month period;
- in addition to the current indications in diagnosis (MBS item 69444), viral detection (qualitative) testing be restricted to patients undertaking antiviral therapy, and used once if needed prior to treatment and up to three times in the following twelve months to assess treatment response; and

- the maximum number of qualitative tests for any course of treatment is 4, including those provided under Item 69444.

The Minister for Health and Aged Care accepted this recommendation on 6 March 2000.

Introduction

The Medicare Services Advisory Committee (MSAC) has reviewed the use of PCR-based forms of testing to predict the response to interferon therapy in patients infected with hepatitis C virus.

MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics and health administration.

This report summarises the assessment of current evidence for the use of PCR-based forms of testing to predict the response to interferon therapy in patients infected with hepatitis C virus.

Background

Hepatitis C viral load testing

The procedure

The tests considered in this report are polymerase chain reaction (PCR)-based tests used in the diagnosis and management of hepatitis C infection. These tests are sophisticated molecular techniques which can detect the ribonucleic acid (RNA) of the virus in a patient's blood. PCR-based techniques can be used in one of three ways:

- to detect if hepatitis C virus is present in a patient's blood. This is termed a qualitative test (the test indicates whether RNA is present or absent). It is used to determine if the virus has been eradicated from a patient after treatment with alpha interferon or combination therapy;

- to detect the level of HCV RNA viral load. This is termed a quantitative test. A higher viral load indicates a higher level of infectiousness. Persons with higher viral loads are less likely to respond to treatment with interferon therapy; and

- to determine the type of hepatitis C virus present. This is termed genotyping. In Australia the most common genotypes are type 1 and type 3. Patients infected with the genotype 3 virus are more likely to respond to interferon therapy than patients with genotype 1 virus.

Intended purpose

The most important clinical use of the above forms of testing is to provide sufficient evidence so that a decision can be made to initiate and/or continue treatment of hepatitis C infection with alpha interferon. It is thought that such testing may provide additional information which may help both patients and clinicians in making such decisions. The qualitative RNA detection test may also be used to evaluate the response to treatment.

Transmission, prevalence and incidence

The hepatitis C virus was first isolated and the first diagnostic assay developed in 1989.[1,2] HCV is a single strand RNA virus with at least six genotypes. HCV is widespread with recent World Health Organisation studies indicating that 3 percent of the total world population is infected. Genotypes 1 and 3 are most common in Australia[3]. The majority of parenterally transmitted non-A, non- B hepatitis has been attributed to HCV infection. Since 1989 there has been tremendous advancement in the development of diagnostic technologies in HCV. The rapid rate of technological advancement has been of clear benefit in the prevention of viral transmission through blood products. However this rapid progress presents data analysis difficulties because studies are hard to compare as technology changes. Nonetheless, it is now clear that transmission occurs almost exclusively through blood-to-blood contact.

The NHMRC report in 1997 estimated there may be more than 80,000 current and former injecting drug users (IDU's) in Australia and that an annual incidence of 8,000 to 10,000 new infections was probable. In Australia, IDU's represent the biggest at-risk group. In a recent report of notifications to the South Australian STD Control Branch[4], 60 percent of all individuals testing positive for HCV reported past and/or current injecting drug use. Other risk categories include a history of blood transfusion and tattoos – together accounting for around 20 percent of individuals testing positive for HCV. Depending on the nature of the procedures performed, health workers have highly variable rates of HCV infection – with higher rates for more invasive procedures and correlated with duration of practice[5]. According to Sharara et al[6], however, the overall prevalence of HCV in health workers is comparable to that of the general population. Mother-to-child, or 'vertical' transmission, has been documented and conflicting evidence for sexual transmission continues to be presented. However, it is likely that these transmission routes make up only a very small proportion of current HCV cases.[7,8,9,10,11] An additional risk factor for acquiring HCV infection is birth or residence in a country where HCV is endemic, and where exposure to contaminated medical instruments or cultural practices such as tattooing are thought to be common modes of transmission.

While household contact with an already infected individual has been reported as a risk factor, incidental exposure through the sharing of toothbrushes, shaving equipment, nail clipping equipment and so on, is thought to be the mechanism of transmission rather than through casual contact.[10,12] A substantial proportion of individuals testing positive for HCV – widely reported to be anywhere between 20 to 40 percent - are unable to identify any risk factor.[13,14,15] Due to the often silent course of chronic HCV infection and the relatively recent ability to detect the virus, there are difficulties in accurately estimating the prevalence and incidence of HCV in Australia. Recent apparent increases in infection rates are likely to be greatly influenced by changes in targeted screening practices. True incident cases may only be identified where negative results for previous tests are available. Also, differences between State and Territory surveillance methods and the non-uniform commencement of mandatory notification present further difficulties in estimating the overall burden of disease in the population. Current estimates suggest that between 0.5 percent and 1.0 percent Australians are chronically infected with HCV[16]. –Nearly 200,000 individuals are affected and up to 11,000 new infections occur per year.[17]

The clinical outcome

Following initial HCV infection, it is estimated up to 85 percent of patients will develop chronic hepatitis while only a small proportion of patients overcome the infection. As discussed by Hoofnagle[18], the prognosis for those chronically infected is highly variable – with many never experiencing any adverse long-term effects at all. However, it is likely that up to 20 percent will develop cirrhosis and a small number of these will develop hepatocellular carcinoma. In most countries, including Australia, HCV is now the most common indication for liver transplantation.[19,20] Using estimates from the recent review by Lowe and Cotton[17], of 11,000 infected persons (the number estimated to be newly infected in Australia for 1997), 8,250 will develop chronic hepatitis. Of these, 880 will develop cirrhosis over the next 20 years, 220 will experience liver failure and 88 will develop hepatocellular carcinoma.

It is also emerging that infection with hepatitis C may be associated with a number of other adverse health states. HCV has been strongly associated with essential mixed cryoglobulinaemia, membranoproliferative glomerulonephritis, porphyria cutanea tarda, autoimmune thyroiditis, and less strongly with Sjögren's syndrome, lichen planus and idiopathic pulmonary fibrosis.[6,21,22,23]

Despite the possibility of serious health consequences, it is clear that a majority of individuals chronically infected with HCV will present with few clinically overt signs. In the absence of such, they tend to be diagnosed as 'healthy carriers'. However, it is now becoming apparent that this description may not always be completely appropriate. Many HCV-infected individuals, for instance, report chronic tiredness, abdominal pain, nausea, muscle and joint pains and depression in the absence of biochemical abnormalities or cirrhosis.[24,25] It is also increasingly proposed that while serum levels of alanine aminotransferase (ALT) may correlate with hepatic damage caused by other types of viral hepatitis, it may be a less useful indicator in HCV[26]. Several studies now report significant histological injury even where ALT remains persistently normal.[23,27,28,29] Serum ALT determinations are of only limited clinical value in determining the presence or absence of significant liver injury in comparison to histological examination of liver tissue.

As mentioned previously, the tests considered in this report fall into three categories:

- qualitative tests;
- quantitative tests; and
- genotyping.

The following is a more detailed explanation of the three types of tests.

CV qualitative (detection) test

Initial detection of HCV infection generally relies on an ELISA (enzyme linked immunoabsorbent assay), with mandatory use of some confirmatory procedures for reactive samples, eg. RIBA (recombinant immunoblot assay). These serological tests detect the presence of HCV antibody in patient serum. The antibodies form a complex with recombinant antigens from structural and non-structural domains of the virus, which are then detected by labelled anti-human IgG[30]. Sensitivity for detecting anti-HCV antibodies using the 3rd generation ELISA test system is approximately 97 percent in high prevalence populations[31]. False positive results can be a problem in low risk populations or for patients with high levels of IgG.

RIBA is used as a supplementary test for ELISA as it utilises the same recombinant viral antigens. It differs from ELISA in that the recombinant HCV antigens are individually immobilised on a nitrocellulose strip[30]. Damen et al[32] suggest that the sensitivity of the assay is 99.5 percent. Two positive bands are considered to be suggestive of viraemia, although correlation with qualitative PCR testing is less than 50 percent; this improves to 84 percent with three and four band reactivity. Approximately 10 percent of RIBA tests give indeterminate results, particularly for immunosuppressed patients.[33] Patlowsky et al observed active viral replication (via PCR detection) in approximately half of 59 patients giving indeterminate RIBA patterns compared with 90 percent of 59 RIBA-positive

patients. Serological tests, on the whole, are easy to use, relatively inexpensive, can be automated and give low variability[34].

PCR-based techniques are increasingly being employed for the detection and diagnosis of viral diseases such as HCV infection. These techniques involve the amplification of DNA templates and can be extremely sensitive in detecting viral levels of less than 100 copies/ml of serum[35]. This makes PCR particularly useful for the early detection (within two weeks of exposure) of the virus[35]. Techniques involving PCR are, however more complex, time consuming and expensive than serological testing.

For HCV, reverse transcription of the highly conserved 5' untranslated region of the viral genome is followed by amplification of the resulting complementary DNA template; this technique is called RT-PCR. As it is a highly sensitive test, RT-PCR can be prone to false positive results due to cross contamination, however in one report[36], false positives were found to be relatively rare, and RT-PCR for detecting HCV RNA was found to be useful when serological assays were indeterminate. False negative results can also be a problem if samples have been stored incorrectly as repeated 'freeze-thaw' cycles can cause degradation of the RNA genome. Some studies indicate that PCR techniques may be employed to detect HCV in body fluids other than blood.

Some patients who are hepatitis C antibody positive do not have detectable levels of HCV RNA. These patients may have levels of HCV RNA below the detection limit of PCR testing, they may have false positive ELISA results or they may have spontaneously resolved their HCV infection. In addition, studies by Kao et al [31] suggest that 6 percent of chronic non-A non-B hepatitis patients (as determined by histological investigation) show no sign of HCV infection based on third generation ELISA and PCR results. They suggest that either these patients have intermittent or fluctuating HCV viraemia or that a non-B non-C agent is involved.

HCV quantitative (viral load) test

Two main molecular techniques exist for the quantification of HCV RNA, namely quantitative PCR methods and signal amplification techniques such as the branched DNA (bDNA) assay. Quantitative PCR utilises competitive RT-PCR involving two simultaneous reactions and incorporating an internal control. The target sequences chosen are generally in the conserved 5' untranslated region of the HCV genome, which is important for sensitivity, specificity and reproducibility[37]. The internal control is a synthetic RNA molecule having the same primer recognition sequence as the HCV target sequence[38]. Intensity of amplification of HCV RNA is then compared to the internal standard of known concentration to determine the relative concentration of HCV. The detection limit of current assays is as low as 100 copies/ml of viral RNA[39]. Some variations of the assay include chemiluminscent probes to differentiate between the control and HCV amplification products.[38, 40]

The Amplicor Monitor assay is a modified RT-PCR assay undertaken in one tube. It is therefore simpler than conventional RT-PCR techniques and has a lower risk of contamination[41]. Colucci and Gutekeunst[39] suggest the assay can detect 10^3 to 10^6 copies of HCV RNA per millilitre of patient serum. Accurate determination of concentrations above 10^6 copies is limited and the assay is highly variable[35]. Hawkins et al[42] found that the Amplicor Monitor assay may have up to ten fold bias in determining viral load for patients having different HCV genotypes.

The bDNA method involves capture of the HCV RNA genome between two oligonucleotide probes targeting the 5' non-coding and coding regions of HCV[43]. This enables direct detection and assessment of the quantity of captured RNA via chemiluminescent signal amplification. The signal directly corresponds to the amount of HCV present and can be detected 82 percent of the time.[45] Although fivefold less sensitive than PCR methods (bDNA detects 5000 – 10^4 copies/ml), this assay avoids the shortfalls of PCR methods, such as contamination problems[45]. The assay is very reproducible, showing only 2 percent variability[46]. Brester et al[44] suggest that bDNA assays should be used in conjunction with quantitative PCR methods in order to minimise misdiagnosis of patients with low viral loads. In general bDNA is more accurate in the higher ranges of viral load than PCR which is more sensitive (lower detection limit) than bDNA, so in clinical trials most investigators use PCR to detect viraemia when bDNA is negative.

Ichijo et al[42] suggest that the Amplicor assay is less sensitive than competitive RT-PCR and more sensitive than the bDNA assay. The RNA range it can detect also falls between competitive RT-PCR and bDNA assays, being 10 times narrower than competitive RT-PCR and 100 times wider than bDNA. Within the reference range HCV RNA concentrations detected by the Amplicor assay correlated with both competitive PCR and bDNA assays[45].

HCV genotype (serotype) test

The hepatitis C virus is subject to significant genetic heterogeneity. It has been observed there is a relationship between genotype and the clinical manifestations of the disease, disease severity and the response to interferon treatment. HCV can be classified into six distinct types with more than 30 subtypes[46]. There are various different assays available to determine HCV genotype; these include serological and PCR-based assays.

PCR-based methods for genotyping HCV are far more extensively used than serotyping techniques, due to their ability to differentiate between subtypes of the virus such as 1a and 1b. Current PCR-based methods utilise one of four broad strategies:

- RT-PCR using type-specific primers;
- sequencing of PCR products;
- RT-PCR of the 5' untranslated region or NS5 followed by analysis of restriction fragment length polymorphisms (RFLP); and
- PCR using universal primers followed by hybridisation of type-specific probes.[47,50]

Lau et al[48] have shown good concordance (94%) between the different techniques, although they also demonstrated that with whatever system is used there is a proportion of patients (3-17%) who can not be genotyped even if serum is collected under optimal conditions. HCV genotyping is limited if serum samples have not been stored correctly or if no viraemia is present[48,51].

RT-PCR using type-specific primers is by far the most common method used to genotype HCV and tends to target the variable regions of the HCV genome, i.e. the

capsid (core) encoding region plus the E2 envelope and NS5 domains. Success of the technique is mainly limited by the specificity of primers to target sequences[49]. PCR techniques can also be biased by the variable efficiency of amplification for some genomic regions[19]. As tests are designed to favour the dominant species of HCV, they may misrepresent (overestimate) mixed infections.

Sequencing, RFLP and LiPA can help to confirm the identity of PCR products. These techniques tend to use PCR products amplified from less variable regions. Sequencing analysis compares the entire length of the viral genome or PCR products. It is both time consuming and expensive and hence not suitable for large numbers of clinical samples. Sequence analysis is quite sensitive to mixed samples and can pick up less dominant variants if they make up greater than 10-20 percent of the mix[48]. RFLP involves the digestion of PCR products using restriction enzymes and allows the comparison of digestion patterns rather than the entire sequence. This method has been shown to give excellent concordance with the LiPA assay[50]. LiPA (line probe assay) uses type specific probes to bind to the PCR product. Both LiPA and RFLP tend to underestimate the prevalence of mixed infections.

Serologic genotyping (or serotyping) assays are not able to discriminate between HCV subtypes and appear to be less effective in immunosuppressed individuals[50]. However, they are relatively simple to use and do not require hepatitis C viraemia at the time of the assay. The two main serotyping methods utilise synthetic peptides based on genotype specific regions of either the core region or NS4 region of the HCV. These peptides then react with different genotype-specific antibodies in patient serum. Lee et al[51] found that serotyping achieved a specificity of 90 percent for genotypes 1, 2 and 3.

More recent developments using RIBA methods incorporating the NS4 region have been successfully used to identify HCV type. Up to 90 percent of cases were successfully serotyped with 99 percent concordance with PCR methods[52]. This method was highly reproducible and reliable; unfortunately serological methods can be limited for early identification as seroconversion is known to occur relatively late after exposure in HCV and fails to occur at all in a small number of individuals[23]. HCV core serotyping methods may be helpful in tracing transmission routes where only serum containing anti-HCV is available[53].

The geographical distribution of genotypes is not uniform throughout the world. In Australia the most common genotypes are 1a, 1b and 3a.

Intended purpose

The most important clinical use of the above forms of testing is to inform the decision to initiate and/or continue antiviral treatment of hepatitis C infection. It is thought such testing may provide additional information that may be of use to both patients and clinicians in making decisions. The qualitative RNA detection test may also be used to evaluate the response to treatment.

Clinical need / burden of disease

Treatment of hepatitis C

Until recently, interferon alpha (IFN-α) was the only drug approved in Australia for the treatment of HCV infection. Specifically, interferon alpha-2b (Intron A – Schering Plough) or alfa 2a (Roferon - Roche) was the standard treatment. Interferon is currently available to specific HCV patients under the nationally funded S100 program for Highly Specialised Drugs (HSD). Under guidelines established at its release by the Federal Government in 1994, relatively strict criteria developed by the Pharmaceutical Benefits Advisory Committee were applied to all patients before its use could be permitted. These criteria have since been slightly modified following the release of the recent NHMRC strategic report into the management of HCV[3]. The report led to the inclusion of patients with concomitant HIV infection and IV drug users, as well as an increase in the approved duration of treatment from 24 to 52 weeks. The current criteria for IFN-α use in HCV are as follows:

- chronic hepatitis evident on liver biopsy (with the exception of individuals with coagulation disorders);
- repeatedly positive anti-HCV test;
- abnormal ALT levels in conjunction with demonstration of viral infection (HCV RNA positive and/or anti-HCV positive);
- no cirrhosis or other liver disease;
- not pregnant, not lactating or at risk of pregnancy;
- no history of significant psychiatric illness;
- likelihood of compliance with treatment and follow-up; and
- drinking below the level of 7 standard alcoholic drinks per week.

Non-responders are not eligible for re-treatment with IFN-α under the existing HSD program criteria.

As part of the conditions for funding, the HSD program subsidy ceases if ALT remains above the upper limit of the laboratory reference range at 12 weeks of treatment. A further condition of funding is that the treatment course is continuous. The strict eligibility criteria are necessary because of the relatively high cost of therapy (a single dose of IFN-α-2b of 3MU in 0.5ml single dose pre-filled syringe currently costs $26.24) combined with the relatively low overall rate of a sustained response to interferon monotherapy.

As of October 1999, combination treatment with IFN-α and the oral antiviral medication ribavirin has been approved under the HSD program in patients who have relapsed after montherapy with IFN-α for the maximum period of 24 weeks. A negative qualitative PCR is essential for funding to continue beyond 12 weeks of therapy,

although the Commonwealth does not currently fund this required testing. The same patient entry criteria as described above apply for combination therapy.

The following table (Table 1) illustrates the end of treatment and sustained response rates for patients treated with interferon alone, combination therapy for 24 weeks, and combination therapy for 48 weeks.

Table 1 Effects of interferon (IFN) plus ribavirin (RBV) in producing a sustained virologic response in previously untreated patients with chronic hepatitis C

	IFN + RBV for 48 weeks	IFN + RBV for 24 weeks	IFN + placebo for 48 weeks
Poynard et al[55] International study, Including 4 Australian centres			
Overall			
ETR	52%	57%	33%
SR	43%	35%	19%
By genotype			
1 or 4	31%	18%	11%
2 or 3	64%	64%	33%
McHutchinson et al[56]			
Overall			
ETR	50%	53%	24%
SR	38%	31%	13%
By genotype			
1	28%	16%	7%
Non -1	66%	69%	29%

The aim in treating HCV infected patients with antiviral therapy is to reduce the number of chronically infected individuals. It is thought this will reduce the number of patients who develop the long-term complications of HCV infection, such as liver failure and hepatocellular carcinoma, although the evidence for this remains uncertain[57]. Instead, many of the trials have investigated sustained loss of viraemia as the primary outcome in addition to secondary outcomes such as histological improvement and ALT normalisation. The most common primary outcome measured in the studies included in this review was normalisation of ALT levels.

The effectiveness of alpha interferon therapy in inducing the normalisation of liver function tests such as ALT is also unclear. Four meta-analyses have been performed which have attempted to answer this question. The first, published in 1991, estimated that approximately 50 percent of patients treated with alpha interferon would achieve a response after 6 months of therapy, but that only 25 percent of patients would achieve a sustained response.[58,59] A meta-analysis published in 1995 estimated that the sustained response rate (based on the results of 27 trials) was 29.95 percent[60], while another meta-analysis based on the results of 21 trials and also published in 1995 estimated the sustained response rate to be 17.4 percent[61]. Poynard et al published a meta-analysis in 1996 in which the proportion of patients with a sustained biochemical response to 3 million IU of interferon for 6 months was 14 - 22 percent which increased to 28 - 38 percent in those treated with the same dose for 12 months or longer[56]. The more important outcome of achieving a sustained virological response was not reported but was likely to have been much lower than the reported biochemical (ALT) responses.

A recent study indicated that interferon therapy significantly reduces the risk of hepatocellular carcinoma, in both cirrhotic and non-cirrhotic patients especially among virologic or biochemical responders[62]. This is one of the first studies to demonstrate that interferon therapy results in an improvement in clinical outcomes, rather than changes in surrogate biochemical or virologic markers.

In Australia few patients have opted for anti-viral treatment of HCV. In 1997 it was estimated that fewer than 4 percent of patients with chronic HCV infection had tried interferon therapy[63]. This may be due to lack of certainty of a positive response to treatment, the perceived side effects or difficulty in access to treatment.

Comparator

The most appropriate comparator for the monitoring of alpha interferon therapy is alanine aminotransferase (ALT), an enzyme released by hepatic cells as a result of damage. There is relatively strong evidence that elevated pretreatment ALT levels are associated with sustained response to IFN-α (elevated pretreatment ALT levels are usually a selection criterion for treatment), as is normalisation of serum ALT by 12 weeks of IFN-α treatment.[64] This review does not propose the assays under evaluation replace ALT monitoring. The review proposes that, if viral factors also prove to be predictive of a response to antiviral therapy, then viral assays could be incorporated in the pretreatment work-up and monitoring of treatment. As such, the addition of the proposed viral assays could potentially assist both clinicians and patients in the decision-making process.

Marketing status of the technology

As of October 1995 all HCV in-vitro diagnostic kits became low-level registrable devices in the Australian Register of therapeutic goods. HCV test kits for first line screening are accessible to all laboratories, however kits approved for supplemental testing, including those based on molecular techniques are authorised for use only in laboratories specified by State health authorities.

Current reimbursement arrangement

Pathology Item 694444:

Detection of hepatitis C viral RNA if at least one of the following criteria is satisfied:

- the patient is hepatitis C sero-positive and has normal liver function tests on two occasions at least 6 months apart;
- the patient's serological status is uncertain after testing;
- the test is performed for the purpose of:
  - determining the hepatitis C status of an immunosuppressed or immunocompromised patient; or

- the detection of acute hepatitis C prior to seroconversion where considered necessary for the clinical management of the patient; not exceeding 1 episode in a 12-month period.

Item 6944 is subject to rule 20:

"Hepatitis C sero-positive" for a patient means two different assays of hepatitis C antibodies are positive.

"Serological status is uncertain" for a patient means any result where two different assays of hepatitis C antibodies are inconclusive.

Approach to assessment

As was explained above, PCR-based forms of testing have limitations in their usefulness for the initial diagnosis of hepatitis C infection (PCR is actually more accurate than serological testing in the initial diagnosis but the ELISA is less expensive and easier to perform). They may prove to be useful, however, in providing information which can guide decision making with regard to the treatment of hepatitis C infection. Information gathered from the PCR tests may allow the treatment of hepatitis C infection to be better targeted towards those patients who are most likely to gain benefit from treatment. The three questions which are the subject of this review are:

- Does pretreatment determination of HCV genotype predict response to interferon therapy in patients with hepatitis C?
- Does pretreatment determination of viral load predict response to interferon therapy in patients with hepatitis C?
- Is detection of viraemia by qualitative PCR during antiviral therapy predictive of a sustained virological response in patients with hepatitis C?

These three questions are attempting to assess the predictive value of PCR-based forms of testing when deciding whether to initiate or continue antiviral therapy of a patient with hepatitis C.

For this type of question, the most methodologically sound form of study is a well-designed prospective cohort study which consists of a clearly defined sample of individuals representative of the population of interest and using objective outcome criteria[65]. In attempting to evaluate the predictive value of a patient characteristic, it is also important to adjust the study to account for other known prognostic factors. This is usually done by means of a multivariate logistic regression analysis. We therefore concentrated our search on studies which involved a multivariate analysis. In order to ensure that each study included a representative sample of patients, we only included studies with more than 30 patients.

Review of literature

The medical literature was searched to identify relevant studies and reviews. The details of the search strategy are outlined in Table 2 below. The initial search strategy resulted in the detection of 2074 citations. The titles of the citations and abstracts where available were scanned for relevance to this review. If there was any uncertainty, the full text was retrieved and assessed for eligibility for inclusion in the review.

Table 2 Details of search strategy

Database	Search terms
1) Cochrane Library up to 2nd issue 1999	Hepatitis C and Interferon-alpha (MESH)
	Hepatitis and interferon (free text)
2) Medline – Silverplatter, 1990 – June 1999	Interferon- alpha (MESH – all subheadings)
	Hepatitis C (MESH – all subheadings)
3) Embase, 1974 – June 1999	Alpha interferon (segments)
	Hepatitis (segments)
4) Current contents, June 1998 – April 1999	Hepatitis and interferon
5) Australasian Medical Index, 1980 – May 1999	Hepatitis and interferon
6) MetaRegister (Controlled Trials), April 1999	Hepatitis and interferon
7) Best Evidence 2, April 1999	Hepatitis and interferon
8) National Research Register (NRR UK), March 1999	Hepatitis and interferon

Inclusion/Exclusion Criteria

The inclusion criteria for this review were studies which were multivariate analyses and which included more than 30 patients. After examining the abstracts or whole text of the articles obtained from the search strategy, we excluded 1880 studies for the following reasons:

Not relevant to question	655
Not a primary study	693
Abstract available only	246
Sample size < 30	153
Univariate analysis only	129
Unable to extract data from article in language other than English	4

Extraction of data

Data were extracted independently by two reviewers. Any differences between reviewers in data recorded or assessment of quality were discussed and/or referred to a third reviewer.

Assessment of quality

Each of the studies included in this review was assessed for quality using the following criteria:

- the inclusion and exclusion criteria for participants were described;
- the study examined a consecutive series or a random selection of a consecutive series of patients; and

- the methods for carrying out the study were described in sufficient detail to permit replication.

The evidence presented in the selected studies was assessed and classified according to the National Health and Medical Research Council (NHMRC) revised hierarchy of evidence shown in Table 3.

Table 3 Designation of levels of evidence

I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies or interrupted time-series with control group.
III-3	Evidence obtained from comparative studies with historical control, two and more single arm studies or interrupted time-series without a parallel control group.
IV	Evidence obtained from case-series, either post-test or pre-test and post-test.

Source: NHMRC[66]

Expert advice

A supporting committee with expertise in clinical and social aspects of viral hepatitis was established to evaluate the evidence and provide advice to MSAC. In selecting members for supporting committees, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations for nominees. Membership of the supporting committee is provided at Appendix B.

Results of assessment

Is it safe?

The assays which are the subject of this review are unlikely to pose an increased risk to patients. The required quantity of serum is minimal and would usually be collected concurrently with other blood tests required during antiviral therapy.

Is it effective?

After following the search strategy outlined above, we were able to identify 105 studies which had included data on the predictive value of the above three forms of testing in HCV infected patients.

Quality assessment

There were a number of problems which we encountered when attempting to extract the data from the studies which we had identified in our search. Some of the problems were:

- outcomes were not defined adequately. For example, the outcome of the analysis may have been reported as response to interferon, but this was not further defined, making it impossible to determine which of the many possible responses was being measured in the report;
- patient details were not described. We excluded studies which did not adequately describe patient characteristics, such as age, sex, and presence of cirrhosis;
- limited details of the multivariate analysis were published in the report, such as which factors were included in the model and which were statistically significant;
- the variables of interest were not included in the analysis; and
- some studies reported unusual statistics with no further explanation. For example, one study reported the results of the logistic regression as relative risk estimates. It was unclear from the details given if the usual result of a logistic regression, the odds ratio, had been converted to a relative risk estimate, or whether the study investigators had misnamed the estimate of the study. Many studies reported only p values, and not odds ratios;

Seventy studies were excluded because of the types of problems described above. Many studies did not report whether the cohort had been studied prospectively or retrospectively. Retrospective cohort studies may be more biased, in that there may be less accurate recording of data, but such studies were not excluded.

Table 4 lists the 35 studies included in the final analysis and shows the type of tests used. Further details of each of these studies, including more specific details on the population studied, the form of interferon therapy used, the tests employed and the outcome are shown in Appendix C. The citation details for the excluded studies are at Appendix D.

Table 4: Studies included in the review

Author	Location	n	Patient subgroup	Genotyping	Viral load	Viral detection
Arase (1994)	Japan	38	Previously treated		*	*
Ascione (1998)	Italy	80	Mixed histology	*		
Brouwer (1998)	Multicentre	336	Mixed histology	*	*	
Chayama (1997)	Japan	110	Genotype 1b, Mixed histology		*	
Chayama (1996)	Japan	38	Non-cirrhotic	*	*	
Chemello (1997)	Italy	92	Previously treated	*		*
Chemello (1995i)	Italy	174	Mixed histology	*		
Chemello (1995ii)	Italy	321	Mixed histology	*		
Di Marco (1997i)	Italy	310	Mixed histology	*		*
Di Marco (1997ii)	Italy	67	Thalassaemia, Mixed histology	*		
Fernandez (1997)	Spain	51	Mixed histology	*		
Gavier (1997)	Spain	187	Mixed histology	*		*
Hayashi (1998)	Japan	311	Mixed histology	*	*	
Imai (1997)	Japan	84	Mixed histology – noncirrhotic		*	
Jenkins (1996)	Australia	49	Mixed histology	*	*	
Kikuchi (1998)	Japan	67	Mixed histology – noncirrhotic	*	*	
Kumada (1996)	Japan	54	Mixed histology	*	*	*
Le Guen (1997)	France	95	Mixed histology	*	*	
Lin (1996)	Australia	65	Mixed histology		*	
Magrin	Italy	100	Mixed histology	*	*	
Martinot-Peignoux (1998)	France	228	Mixed histology	*	*	
Martinot-Peignoux (1995)	France	141	Mixed histology	*	*	
Matsumoto (1994)	Japan	36	Mixed histology	*	*	
Nomura (1997)	Japan	50	Mixed histology – unstaged	*	*	
Papatheodoridis (1996)	Greece	60	Mixed histology	*		
Pawlotsky (1998)	France	101	Mixed histology		*	
Pawlotsky (1996)	France	113	Mixed histology	*		
Rumi (1996)	Italy	234	Mixed histology	*	*	
Sartori	Italy	31	Mixed histology	*		
Shiratori (1997)	Japan	272	Mixed histology – noncirrhotic	*	*	
Soriano (1996)	Spain	53	Coinfection – HIV		*	
Toyoda (1996)	Japan	63	Mixed histology	*	*	
Toyoda (1997)	Japan	62	Mixed histology	*	*	
Tsubota (1996)	Japan	185	Mixed histology	*	*	
Tsubota (1993)	Japan	149	Mixed histology	*		

Review results

The results from each of the studies which met our inclusion criteria were extracted by two reviewers working independently and checked for accuracy.

These are summerised in the tables appearing in Appendix E and include studies which conducted multivariate analyses reporting odds ratios for at least one of the three types of testing. The following synopsis is an interpretation of these results, addressing each of the three questions posed earlier in this review.

It should be kept in mind that several studies conducted multivariate analyses of response to interferon therapy for which odds ratios for PCR-based testing were not reported. It is possible that the following summary is biased by only including those estimates from studies which found PCR-based testing to be a statistically significant predictive factor.

Question 1: Does pretreatment determination of HCV genotype predict response to interferon therapy in patients with hepatitis C?

Conclusion: Genotype is not a sufficient indicator of response to exclude a patient from interferon therapy.

Reasoning: From the results shown in Tables 5 to 8 in Appendix E, it is clear there is considerable variation among the studies in their estimate of the association between HCV genotype and response to interferon therapy. The clearest trend indicates the odds of a sustained response to interferon therapy is reduced in patients who have genotype 1a and 1b. We performed a meta-analysis of the odds ratios for genotype 1 versus other genotypes. The pooled estimate of the odds ratio was 6.1 (95% confidence interval of 4.2 to 8.0). The observed heterogeneity is confirmed by the Cochran's Q statistic which is highly significant (89.3 with 17 df, $p < .001$). The pooled result is consistent with previous estimates. The odds ratio of a sustained response to interferon treatment for patients infected with subgroup 3a compared to 1b was estimated to be 6.5 by Martinot-Peignous in 1998[67] and 33.5 by Martinot-Peignous in 1995[68]. For the reasons discussed above, it is likely that this result is an over-estimate of the "true" odds ratio.

To illustrate how these odds ratios affect the probability of responding to interferon monotherapy, we have combined the estimate of the odds ratio with a recent meta-analysis of the effectiveness of interferon therapy[56] and an estimate of the proportions of patients with each genotype in Australia[69]. The pooled estimate of sustained response rates for patients treated with 3 million international units three times per week for 12 months was 28 percent to 38 percent. If it is assumed that the overall response rate is 28 percent and that the proportion of the infected population which is genotype 1 is 60 percent, the estimated sustained response rate in patients with genotype 1 is 11 percent and in patients with other genotypes is 44 percent. If the overall sustained response rate is assumed to be 38 percent, the estimated rate in patients with genotype 1 is 17 percent and in patients with other genotypes is 55 percent. If the true odds ratio is actually less than 6.0, the sustained response rate in both the genotype 1 and other groups will be closer to the average rate. What is significant from these calculations is that even though genotyping is predictive of response to interferon therapy, a proportion of patients with genotype 1 will respond to therapy.

One study has suggested that the observed association between genotype and response to interferon therapy is due to the association between duration of infection and genotype[70]. This study has followed a prospective cohort of 838 patients with chronic hepatitis C infection. The genotype was significantly associated with duration of infection and mode of transmission, but did not affect mortality or the rate of hepatocellular carcinoma.

A further important question is whether genotype is an important predictor of response to combination therapy (a combined regimen of interferon and ribavirin). This therapy is more effective than interferon therapy alone but is also considerably more expensive. It has recently been funded for those persons who have relapsed following a course of interferon therapy. There were no studies which fulfilled our eligibility criteria for this review which examined the value of PCR based testing in predicting the response of patients to combination therapy. A study of 277 patients in 1998 found that genotype was a significant predictor of response to combination therapy. The sustained response rate in patients treated for 24 weeks with genotype 2 or 3 was 64 percent, compared with a response rate of 18 percent for genotypes 1, 4, 5 or 6.

The two largest multicentre studies of interferon and ribavirin (McHutchison et al, NEJM, 1998 and Poynard, et al, Lancet, 1998) are cited in reference list. These studies included over 1700 previously untreated patients and investigated the effects of a number of host and viral factors, including genotype and viral load. In addition, a recent re-analysis by the same authors has investigated the role of genotype and viral load by logistic regression[72].

Question 2: Does pretreatment determination of viral load predict response to interferon therapy in patients with hepatitis C?

Conclusion: The results indicated that viral load titre is predictive of a response to interferon therapy, but is not sufficient an indicator that patients should be excluded from a trial of therapy on the basis of the results of viral load testing.

Reasoning: Again, there is an obvious trend that patients who have a lower initial viral load have much higher odds of a response to therapy, but the estimate of such a response is quite heterogeneous (refer Tables 9 to 11 Appendix F). A pooled odds ratio of sustained response in patients with low versus high viral load titres (the studies in Table 9) is 11.8 (95% CI 4.7 to 16.8). The degree of heterogeneity is even greater than with viral genotyping, however ($Q = 8.3.6$ with 18 df, $p<.0001$). One reason for the degree of heterogeneity is the variation between the studies in the values used as the cut-off for high versus low levels of viral load titre.

Question 3: Is detection of viraemia by qualitative PCR during antiviral therapy predictive of a sustained virological response in patients with hepatitis C?

Conclusion: It is appropriate to use this test to decide if interferon therapy should be continued in an individual patient.

Reasioning: The detection of HCV RNA at either 1 month into treatment or at the end of treatment significantly reduces the odds of a sustained response to therapy. The pooled odds ratio for the studies in Table 12 Appendix G is 27.5. Despite the wide confidence interval observed in each individual trial, the test of heterogeneity in this case is not significant ($Q = 3.7$ with 2df, $p = 0.15$). Even though there are only a few studies

which have been included for this question, the studies show consistent results and a highly statistically significant result.

A further question is whether qualitative detection tests are predictive of the clinical course of disease after interferon treatment. The recently published study by Yoshida[63] shows that patients who had both a sustained biochemical and virological response to interferon therapy had a reduced risk of hepatocellular carcinoma. Approximately 17 percent of patients treated with interferon had a sustained biochemical response (normal ALT levels) but a positive HCV RNA detection test, implying that the virus was not completely eliminated. Relative risk of hepatocellular carcinoma in this group of patients, (with the reference risk of patients who had not been treated with interferon as 1.0) was raised compared with the relative risk in patients with both a sustained biochemical and virological response (0.271 compared with 0.17). The qualitative detection test therefore does provide additional prognostic information regarding the long term clinical outcome.

The studies suggest the lower risk of developing HCC is an interferon effect which is independent of viral clearance (probably related to the antiproliferative effects of interferon) although most studies show a stronger protective effect in sustained virological responders.

Discussion

Determination of HCV genotype and viral load prior to treatment are predictive of the response to interferon therapy. A proportion of patients in the categories which are less likely to respond to therapy may have a sustained response to therapy and the results of the tests should not be used to exclude patients from interferon therapy. The estimates from the different studies show marked heterogeneity. This reflects the considerable variation in the patient populations, the treatment used and its duration, and the way that patients were classified.

The review of the third question shows that a viral detection test after 4 weeks or 12 weeks of interferon therapy is highly predictive of the long-term response to therapy with interferon alone. Very few patients who have detectable levels of HCV RNA at this time will have a sustained response to treatment.

The international standard of therapy is now a combination of interferon plus ribavirin. The "cutoff point" appears to be different for combination therapy. A "cutoff point", in this case at 24 weeks, is probably a better option and would allow a greater proportion of patients to achieve a sustained virological response[74].

The estimates in our current report are likely to overestimate the predictive value of PCR-based testing. This is because studies which included these variables in a multivariate analysis but which found they were not statistically significant may not have stated this in their published results.

What are the economic considerations?

Hepatitis C is a serious public health issue and it has been estimated that there are at least 150,000 carriers of the virus in Australia with an incidence of disease of approximately

10,000 cases a year[73]. The costs of the tests are also significant. Because of this it is important to evaluate the economic significance of any change in management.

This assessment looks at the economic effects in the context of interferon monotherapy. Improved response rates occur with the combination therapy. Combination therapy has been shown to be a cost-effective alternative to monotherapy in a UK study.

The cost of the tests which have been quoted in the application were:

- Qualitative detection test $80
- Viral load testing $200
- Genotyping $110

These are the values which have been used in the economic evaluation below. There is currently a fee on the Medicare Benefit Schedule for the HCV detection test which is set at $90. The fee on the Medicare Benefit Schedule for viral load testing for HIV is currently $176.

The qualitative detection test

The qualitative detection test is used to detect an early response to interferon therapy and can be used to guide the decision whether to continue anti-viral treatment. Because of the relative cost of the test ($80) versus the relative cost of continuing treatment ($2800 for 6 months)[74], the test would only have to result in a small proportion of patients ceasing treatment to be cost saving (2.9% at 6 months). What is less certain is the optimal timing of the qualitative test. Unpublished data from Chiron diagnostics indicates the most cost-effective strategy is for testing to occur at 4 weeks. We do not have, however, the primary data necessary to evaluate the marginal cost-effectiveness of the timing of the test. This would require knowledge of the relationship between the RNA detection test at specific points of time and the sustained response rate. Further data are available regarding timing of testing for combination therapy[74].

Viral load testing and genotyping

The potential costs and consequences of viral load testing and genotyping prior to interferon therapy are less obvious. To evaluate this a simple model was developed to attempt to estimate the economic costs and consequences of testing.

The initial model compared the impact of genotyping and viral load testing with an empirical trial of therapy and a qualitative detection test at 12 weeks, at which time a decision would be made whether to continue interferon therapy or not based on the results of the qualitative test. The initial model is shown in Figure 1(shown on Pg 24). The aim of the model was:

- to estimate the expected costs of the alternative strategies;
- to estimate the expected number of patients achieving a sustained response using each strategy; and

- to estimate the "threshold" proportion of patients deciding not to have interferon therapy as a result of testing, at which point testing becomes cost-saving.

Assumptions used in the model

The effectiveness of interferon therapy

The probability of a sustained response to 12 months of interferon therapy of 3 millions international units three times a week was derived from the meta-analysis by Poynard et al (1996)[56]. The base rate was set at 33 percent with a low response rate of 28 percent and a high rate of 38 percent.

The percentage of patients with a negative RNA test at 12 weeks who would achieve a sustained response to interferon therapy was estimated to be a base rate of 43 percent, with a low value of 33 percent and a high value of 53 percent. This data is derived from unpublished data prepared by KF Villa et al of Chiron Diagnostics.

The effectiveness of combination therapy

The probability of achieving a sustained response rate with combination therapy after 24 weeks is derived from the study by Poynard et al (1998)[72]. This estimated a response rate of 35 percent. There is probably an over-estimate of the response rate in this model, as the patients in the study were treatment naive.

Combination therapy has only recently been introduced in Australia. Is it therefore difficult to predict what proportion of patients who have relapsed following interferon therapy will proceed to combination therapy. The model is quite sensitive to estimates of this proportion, however, because of the relatively high cost of combination therapy. It was felt that only a small proportion of patients would proceed on for further treatment. The base rate was set at 10 percent, with a sensitivity analysis from 5 percent to 20 percent.

The proportion of patients deciding not to have interferon therapy

In the initial model, the proportion of patients who had genotyping and viral load testing was set at a base rate of 6 percent and varied between 0 percent and 30 percent. A threshold analysis was also conducted to determine at what level of this variable did the model become cost saving.

The proportion of patients who achieved a short term response to therapy was adjusted to account for the fact that most of the patients who did not proceed to therapy after the testing would belong to groups which had a lower response rate to therapy. This rate was increased such that the proportion of patients achieving sustained response rate was increased by 0.85 times the probability of deciding not to have interferon therapy.

Cost estimates

The expected costs of the test are described above. The cost of interferon therapy and normal medical care were obtained from a recent study of the cost-effectiveness of interferon therapy in Australia[75]. The cost of combination therapy was derived by calculating the pharmaceutical costs of interferon and combination therapy. The marginal cost of combination therapy was then added to the estimate of six months of interferon

therapy used in the paper by Shiell et al[75]. The costs used in the model are summarised below:

• Viral load test	$200
• Genotyping test	$110
• Qualitative test	$80
• Costs of patients deciding not to have interferon (ie expected medical costs for 18 months)	$608 ($300-900)
• Costs of interferon therapy for 3 months (including those who have discontinued treatment) plus 15 months of normal medical care	$1907 ($1238-$2565)
• Costs of interferon therapy for 12 months (including those who have discontinued treatment) plus 6 months of normal care	$5350 ($3720-$6970)
• Costs of combination therapy for 24 weeks	$9916 ($9400-$10746)

Results

Estimates of the costs of testing

Using the base rate estimates with a probability of deciding not to have interferon therapy based on the results of testing of 6 percent, the expected cost for those having interferon therapy was $8,697. The expected cost for those having an empirical trial of therapy with a qualitative detection test at 12 weeks was $8,466. The marginal cost of testing in this model is therefore $231 per patient. At present, approximately 1,000 patients a year are commencing interferon therapy, which would result in a cost of $231,000 per annum if qualitative detection tests were used. The prospect of being able to predict the response to therapy with greater certainty might encourage some patients with hepatitis C infection to consider interferon therapy. This is not likely to alter the marginal cost per patient but may increase the total cost of testing and interferon therapy. If all patients newly diagnosed with hepatitis C infection were to access testing, the total cost would be $3,100,000 per annum.

The model is not highly sensitive to the proportion of patients deciding not to have interferon therapy as a result of testing. This is because of the much higher relative costs of interferon and combination therapy.

Threshold analysis

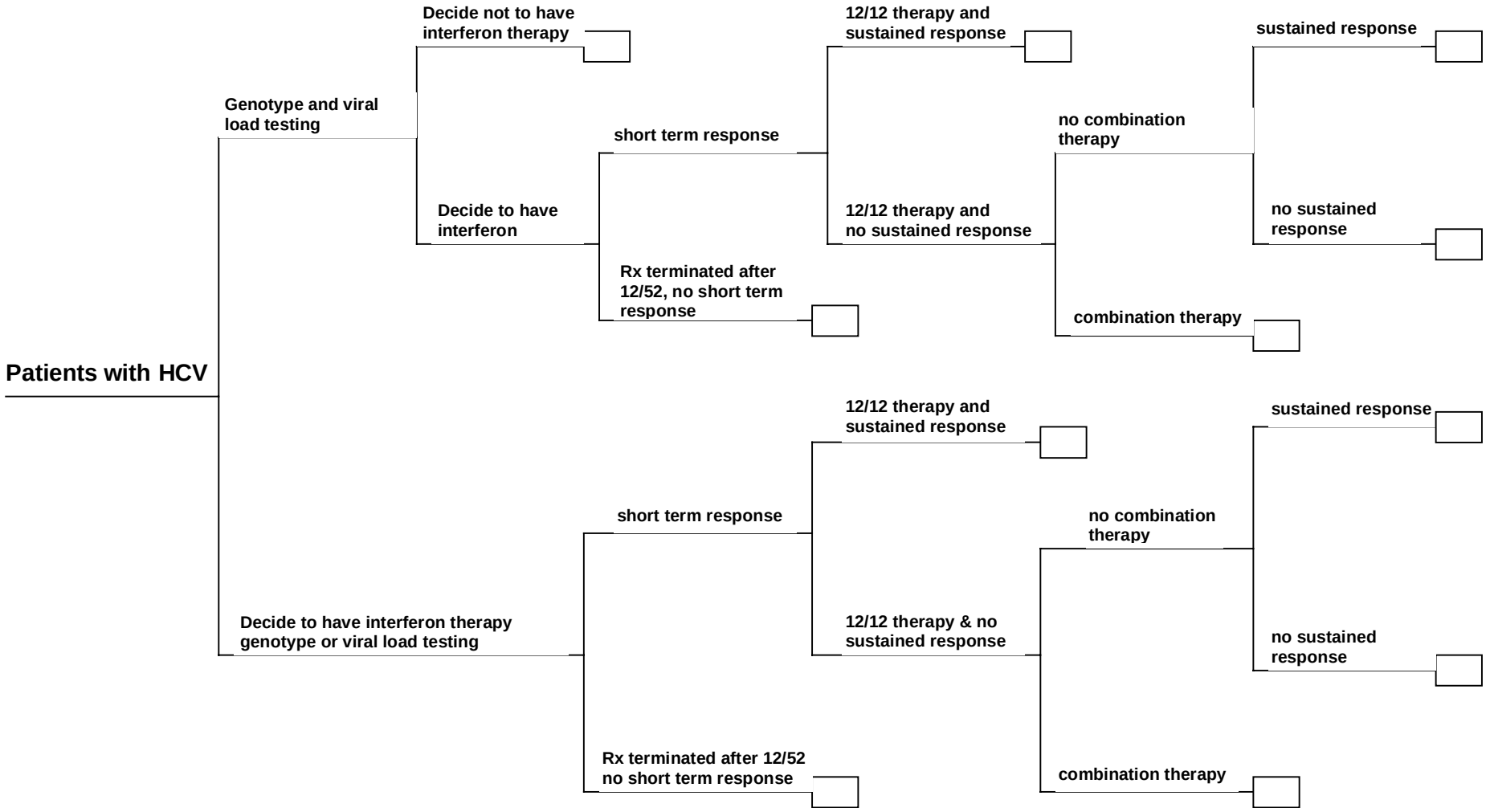
The threshold proportion of patients who it would be necessary to decide not to have interferon therapy as a consequence of testing for the model to become cost-saving is 15 to 16 percent. The proportion of patients who have genotype 1, 4, 5 or 6 or who have high viral load titres is greater than 60 percent. It would therefore not be unreasonable to

predict that providing testing may be cost saving or at most may only have a small impact on total costs, if there is an adequate way of selecting patients for testing.

Consequences of testing

As was explained in the results section above, testing is predictive of a response to therapy, but some patients who have a lower probability of a response to interferon therapy will still respond. By providing testing, a proportion of patients who would have responded to interferon or combination therapy will choose not to undergo treatment. Using the base rate assumptions, with a probability of not proceeding with therapy of 6 percent, the model predicted that of 1000 patients tested, the expected number of patients responding to therapy would only decrease by 2. Even if 30 percent of patients elect not to go ahead with interferon therapy after testing, the number of patients who might otherwise have responded to therapy only decreases by 25. On the other hand, the greater certainty of predicting a response to therapy may encourage some patients who would not otherwise consider therapy to be tested so that the actual number of patients benefiting from anti-viral therapy may increase.

Figure 1 **Comparing the Impact of Genotype and Viral Load Testing and Interferon Therapy Without Genotype or Viral Load Testing**



Other considerations

Combination therapy

- Recent reviews support the view that combination therapy has a higher response rate than monotherapy and cost-effectiveness studies in the UK have strongly supported such treatment. In 1999, the Scottish Health Purchasing Information Centre recommended that 'combination therapy should replace treatment with interferon alone in chronic hepatitis C'. They found there is now good evidence that interferon alfa plus ribavirin is more effective than interferon alone in patients who have not previously received antiviral treatment. Those with three or more factors that predict a good response to treatment should receive interferon plus ribavirin for 6 months. Those with two or less factors predicting response should receive combination therapy for twelve months

- there is also good evidence that six months combination therapy is more effective than 6 months interferon monotherapy in those who have relapsed;

- the estimated marginal cost per life year saved varies between £3000 and £10,000 and is within the range of other accepted NHS activities;

- combination therapy has an acceptable safety profile but requires regular monitoring for early detection of the recognised side effects; and

- there are still many uncertainties in the management of hepatitis C and ideally treatment should be limited to specialist centres with agreed management protocols with detailed information collected on all patients treated.

Access to technology

The value of PCR-based testing is informing clinicians and patients of the probability of achieving a sustained response to interferon therapy. Therefore it is only appropriate to use this testing in patients who are actually considering interferon therapy, and not in all patients infected with hepatitis C. For this reason, consideration should be given to restricting access to those specialty clinics which are able to prescribe interferon therapy. This needs to be balanced against the problem of access to testing, particularly in areas where there is difficulty in accessing a specialty clinic, such as rural areas.

Conclusions

Safety

The tests considered in this review would normally be conducted at the same time as other serological tests used to evaluate the status of a patient with hepatitis C infection. As such there are no additional safety issues concerned with the test.

Effectiveness

Genotyping and viral load titre prior to interferon therapy are both predictors of the response to interferon therapy. The predictive value of these two tests, however, is such that patients should not be denied access to interferon therapy on the basis of these results. They may, however, be used to guide decision making with regard to the likely success of interferon therapy.

The qualitative viral detection test used after at least four weeks of interferon therapy does have a high predictive value for predicting a sustained response to therapy. Patients who have detectable HCV RNA after four or more weeks of interferon monotherapy are unlikely to benefit from continued therapy. However, the timing is different for combination therapy and 24 weeks may be a more appropriate time for determining treatment continuation.

Cost-effectiveness

The qualitative detection test is likely to be cost-saving because of the relative cost of the test versus the high cost of continuing interferon therapy.

Viral load testing and genotyping are likely to be cost saving if the proportion of patients deciding not to commence interferon therapy as a result of the test is greater than 15 percent. This is not an unreasonable assumption, given the proportion of patients who fall into groups with a lower probability of a response to therapy. This model relies, however, on only selecting those patients for testing who would otherwise be considering treatment with anti-viral therapy.

Recommendation

MSAC recommended that on the strength of evidence pertaining to Hepatitis C Viral Load Testing (MSAC Application 1021) public funding should be supported for these procedures as follows:

- The request for these tests should be restricted to consultant physicians who will manage the treatment and should only be used for patients with confirmed hepatitis C (by ELISA or PCR test) who undertake antiviral therapy depending on the result of testing.

MSAC further recommended that:

- genotype testing be restricted to once only for each patient;
- viral load testing be used prior to treatment, and be restricted to once only in any 12 month period; and
- in addition to the current indications in diagnosis (MBS item 69444), viral detection (qualitative) testing be restricted to patients undertaking antiviral therapy, and used once if needed prior to treatment and up to three times in the following twelve months to assess treatment response.

The maximum number of qualitative tests for any course of treatment is four including those provided under Item 69444.

- The Minister for Health and Aged Care accepted this recommendation on 6 March 2000. -

Appendix A MSAC terms of reference and membership

The terms of reference of MSAC are to advise the Commonwealth Minister for Health and Aged Care on:

- the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness; and
- references related either to new and/or existing medical technologies and procedures.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise
Professor David Weedon (Chair)	pathology
Ms Hilda Bastian	consumer health issues
Dr Ross Blair	vascular surgery (New Zealand)
Mr Stephen Blamey	general surgery
Dr Paul Hemming	general practice
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Mr Alan Keith	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Aged Care
Dr Richard King	Gastroenterology
Dr Michael Kitchener	nuclear medicine
Professor Peter Phelan	Paediatrics
Dr David Robinson	plastic surgery
Ms Penny Rogers	Assistant Secretary, Diagnostics and Technology Branch, Commonwealth Department of Health and Aged Care (until 3 May 1999)
Associate Professor John Simes	clinical epidemiology and clinical trials
Dr Bryant Stokes	neurological surgery, representing the Australian Health Ministers' Advisory Council (from 1 January 1999)

Appendix B Supporting committee

Supporting committee for MSAC application 1021
Hepatitis C viral load testing

Mr Stephen Blamey (chair) BSc, MBBS, FRACS Surgeon, Monash Medical Centre Melbourne, VIC	member of MSAC
Professor Robert Batey MD, MB, BS, BSc (Med) FRACP, FRCP (UK) Director Gastroenterology Dept John Hunter Hospital Newcastle, NSW	nominated by the Royal Australasian College of Physicians
Professor Chris Burrell BSc, MB, BS, PHD, MRC Path (UK) FRCPA, FRC Path (UK) Senior Director, Infectious Diseases Laboratories IMVS Dept Microbiology and Immunology University of Adelaide, SA	co-opted member; also nominated by the Royal College of Pathologists of Australasia
Dr William Butson MB, BS, FRACGP, Grad Dip OSH (WAIT) Annerley, QLD	nominated by the Royal Australian College of General Practitioners
Prof Geoff Farrell MD, FRACP Robert W Storr Professor of Hepatic Medicine Westmead Hospital, NSW	nominated by the Royal Australasian College of Physicians
Mr Martyn Goddard Member of and consultant to ANCHARD (Australian National Council on Hepatitis C, AIDS and Related Diseases)	nominated by the Australian National Council on Hepatitis C, AIDS and Related Disesases
Dr Michael Harrison BSc, MBBS, FRCPA Microbiologist, Sullivan Nicolaides Pathology Taringa, QLD	co-opted member
Mr Jack Wallace Executive Officer, Australian Hepatitis Council Grad Dip Health Sciences (HIV Studies) University of Western Australia	consumer representative, nominated by the Consumers' Health Forum

Appendix C Details of Studies included in the review

Arase Y, Kumada H, Chayama K et al. J Gastroenterol 1994; 29: 299-304

Physical Location	Toranomon Hospital, Tokyo JAPAN
Participant characteristics	38 adults, 30 male & 8 female, mean age 46.7, previously treated with IFNβ Excluded: corticosteroid, immunosuppressive, antiviral therapy prior 6 months; positive HBsAg, HBV-DNA, antinuclear Ab; antimitochondrial Ab; wbc > 3500/□ L; platelet > 120000/□ L
HCV test methods	Viral detection: qualitative RT-PCR HCV Genotyping: type-specific RT-PCR
Treatment	6 MU human lymphoblastoid IFN□ (Sumitomo Pharmaceutical Co): 1. daily 8 weeks then twice weekly 16 weeks; 2. twice weekly 48 weeks; 3. daily 8 weeks
Outcomes	Complete response is normalised ALT (<25KU) and negative HCV-RNA at least 6 months post IFN therapy
Variables used in model	Age; sex; IFN schedule; liver histology; previous treatment schedule; ALT response at end of previous treatment

Ascione A, De Luca M, Canestrini C et al. Ital J Gastrolenterol Hepatol 1998; 30: 517-523

Physical Location	"A. Cardarelli" Hospital, Napoli; Civil Hospital, Caserta; Civil Hospital, Foggia ITALY
Participant characteristics	80 adults, 49 male & 31 female, 18-60, mean age, chronic hepatitis and cirrhosis Excluded: low grade liver inflammation; immunosuppressive or antiviral therapy; chronic disease; other causes of hepatic damage; cirrhotic patients with bilirubin>51□ Mol/L; albumin <30g/l; platelet<100,000/□ L; leukocyte<3,000/□ L; oesophageal varices F2-F3 degree; liver decompensation; positive anti-nuclear, mitochondrial, smooth-muscle, LKM autoAb, HBsAg, anti-HIV; pregnancy or pregnancy risk; age>60; hepatocellular carcinoma; decompensated diabetes; homosexual men; drug abuse
HCV test methods	Viral detection: RT-PCR (details not given) HCV Genotyping: RT-PCR (details not given)
Treatment	IFN□ -2b (Intron A, Schering-Plough): 1. 3MU thrice weekly for 12 months; 2. 6MU thrice weekly for 12 months
Outcomes	Long term response was normal ALT 2 years post IFN
Variables used in model	Age; mode of infection; baseline serum ALT, AST, GGT, platelet count, albumin; IFN schedule; duration of chronic liver disease; liver histology

Brouwer JT, Nevens F and Kleter B et al. J Hepatol 1998; 28: 951-959 (BENELUX TRIAL)

Physical Location	Erasmus University Hospital – Dijkzigt, Rotterdam and Academic Medical Centre, Amsterdam, THE NETHERLANDS; Gasthuisberg University Hospital, Leuven, University Hospital, Ghent, Erasme University Hospital, Brussels, St Josephs Hospital Gilly and Saint-Luc University Hospital, Brussels, University Hospital, Antwerp, University Hospital, Liege, Free University Hospital, Brussels, BELGIUM; Central Hospital, LUXEMBOURG
Participant characteristics	336 adults, 200 male & 136 female, 18–70, mean age 47, mixed histology Excluded: additional causes of chronic liver disease; positive HBsAg; >150g weekly alcohol; ferritin >1000 g/L; autoAb>1:100; prior antiviral pr immunosuppressive therapy; decompensated liver disease; cytopenia; HIV; hepatocellular carcinoma
HCV test methods	**Viral detection: qualitative RT-PCR** HCV Quantification: RT-PCR plus hybridisation & bDNA (Quantiplex 1.0, Chiron) HCV Genotyping: LiPA (Inno-LiPa, Innogenetics) & sequence analysis
Treatment	Recombinant INF -2b (Intron-A, Schering Plough): 1. 3MU thrice weekly for 24 weeks; 2. 6MU thrice weekly 8 weeks then 3MU thrice weekly minimum 8 weeks then 1MU thrice weekly minimum 8 weeks (maximum length of therapy was 52 weeks)
Outcomes	**Sustained response was normal ALT levels and negative HCV RNA 6 months post IFN therapy**
Variables used in model	Age; GGT level; cirrhosis; IFN dose; baseline ALT to AST ratio; baseline serum ferritin.

Chayama K, Tsubota A, Kobayashi M et al. Hepatol 1997; 25: 745-749

Physical Location	Toranomon Hospital, Tokyo JAPAN
Participant characteristics	110 adults, 78 male & 31 female, 24-66, mean age 47, genotype 1b Excluded: positive HBsAg, HIV; prior immunosuppressive or antiviral; cirrhosis
HCV test methods	Viral detection: qualitative RT-PCR HCV Quantification: ELISA, bDNA (HCV RNA 2.0, Chiron) HCV Genotyping: PCR-based genotyping and sequencing
Treatment	6MU lymphoblastoid IFN daily for 8 weeks then thrice weekly for 16 weeks
Outcomes	Response was normal ALT and negative HCV RNA 6 months post IFN
Variables used in model	Pretreatment with prednisolone

Chayama K, Tsubota A, Kobayashi M et al. Hepatol 1996; 23: 953-957

Physical Location	Toranomon Hospital, Tokyo JAPAN
Participant characteristics	38 adults, 37 male & 10 female, 22-65, mean age 52, active hepatitis without cirrhosis Excluded: cirrhosis; positive HepB or HIV; immunosuppresive or antiviral therapy prior 6 months
HCV test methods	Viral detection: 2nd generation ELISA (Ortho Diagnostics) and qualitative RT-PCR HCV Quantification: bDNA (Chiron Corp) HCV Genotyping: NS5 type-specific primers

Treatment	1. 40mg/d prednisolone for three weeks, four weeks observation, 6MU lymphoblastoid IFN□ for 8 weeks then 6MU twice weekly for 16 weeks; 2. 6MU lymphoblastoid IFN□ for 8 weeks then 6MU twice weekly for 16 weeks
Outcomes	Response was normal ALT and negative HCV RNA 6 months post IFN
Variables used in model	Age; sex; mode of infection; baseline serum ALT, GGT, iron; body weight; amino acid substitutions in ISDR; liver histology

Chemello L, Cavalletto L, Donada C et al. Gastroenterol 1997; 113: 1654-1659

Physical Location	Pordenone Hospital, Sacile Hospital, Trieste-Cattinara, ITALY
Participant characteristics	92 adults, 94 male & 21 female, 18-55, mean age 47, previously treated Excluded: age>55, ALT<2.5 normal, alcoholism; metabolic disorders; positive HBsAg, anti-HIV, autoAb; HCV RNA negative; decompensated cirrhosis; cytopenia; history of ascites, bleeding varices, hepatic encephalopathy
HCV test methods	Viral detection: ELISA (Ortho Diagnostic Systems), RIBA-3 (Chiron) & qualitative RT-PCR HCV Quantification: signal Amplification System (Quantiplex, Chiron) HCV Genotyping: dot-blot hybridisation with type-specific probes
Treatment	Human lymphoblastoid IFN□ : 1. 3MU thrice weekly for 6 months; 2. 6MU thrice weekly for six months; 3. 6MU thrice weekly for six months then 3MU thrice weekly for 6 months
Outcomes	Sustained response was normal ALT and negative RNA 12 months post IFN
Variables used in model	Age; baseline serum ALT, GGT; liver histology; IFN schedule; disease duration.

Chemello L, Cavalletto L, Bonetti R et al. J Viral Hepatitis 1995ii; 2: 91-96

Physical Location	Pordenone Hospital, Sacile Hospital, Venice Hospital, ITALY
Participant characteristics	321 adults, 220 male & 101 female, 18-65, mean age 46, mixed histology Excluded: cirrhosis of Childs grade B&C; positive HBsAg, anti-HIV, autoAb; drug addiction, alcohol>50g daily; serious illness, major contraindications to IFN Viral detection: ELISA (Ortho Diagnostic Systems), RIBA-2 (Chiron) & qualitative RT-PCR HCV Genotyping: dot-blot hybridisation with type-specific probes
Treatment	Recombinant IFN□ -2a (Roferon-A, Hoffman-La Roche) 3MU or 6MU thrice weekly for 6 or 12 months; 3MU human leukocyte IFN□ (Alfaferone, Alfawasserman): 1. Thrice weekly for 6 months; 2. Daily for 3 months then thrice weekly for 3 months
Outcomes	Sustained response was normal ALT 12 months post IFN
Variables used in model	Age; sex; baseline serum AST, ALT, GGT; liver histology; IFN schedule; disease duration; anti-HCV reactivity.

Chemello L, Bonetti R, Cavelletto L et al. Hepatology 1995i; 22: 700-706 (TriVeneto Viral Hepatitis Group)

Physical Location	Pordenone Hospital, Sacile Hospital, Venezia-Mestre Hospital, S. Vito al T. Hospital, Trieste University Hospital, Udine Hospital, Bolzano Hospital, Padova Hosptial, Cittadella Hospital, Mirano Hospital, Venice Hosptial, ITALY

Participant characteristics	174 adults, 122 male & 49 female, 21– 65, mean age 44, mixed histology Excluded: prior immunosuppressive, steroid, antiviral therapy; pregnancy/lactating; serious illness; drug abuse; alcoholism; positive HBsAg, anti-HIV, autoAb; creatinine>1.7mg/dL; platelet<100000/L; wbc<3000/L; granulocyte<1500/L; advanced/decompensated cirrhosis
HCV test methods	Viral detection: ELISA (Ortho Diagnostic Systems), RIBA (Chiron) & qualitative RT-PCR HCV Genotyping: dot-blot hybridisation with type-specific probes
Treatment	Recombinant IFN -2a thrice weekly: 1. 6MU 4 months, 3MU 8 months if normal ALT or 6MU 6 months then 9MU 1 month if still not normal ALT; 2. 3MU 12 months; 3. 6MU 6 months
Outcomes	Sustained response if normal ALT 12 months post IFN
Variables used in model	Age; sex; baseline serum ALT; body weight; duration of infection; liver histology

Di Marco V, Lo Iacono O, Almasio PL et al. J Med Virology 1997i; 51: 17-24

Physical Location	Clinica Medica I, Palermo ITALY
Participant characteristics	300 adults, 200 male & 100 female, 18-60, mean age 47.8, mixed histology Excluded: advanced cirrhosis; positive HBsAg, anti-HIV 1/2, autoAb; hepatocellular carcinoma; cytopenia; drug addiction; alcohol > 80g/day; prior IFN or other antivirals; contraindications to IFN
HCV test methods	Viral detection: ELISA, RIBA (Ortho Diagnostics) & qualitative RT-PCR HCV Genotyping: NS4 type-specific primers and serotyping
Treatment	10 MU recombinant IFN -2b (Intron-A, Schering Plough) thrice weekly for 8 weeks then 5MU thrice weekly for 18 weeks. Responders then either no treatment or 5MU thrice weekly for 26 weeks
Outcomes	Sustained response was normal ALT for at least 12 months post IFN
Variables used in model	Age; sex; baseline serum ALT, GGT, leukocyte and platelet count, albumin and gammaglobulin; prothrombin time; ALT normalisation rate 4 weeks treatment.

Di Marco V, Lo Iacono O, Almasio PL et al. Blood 1997ii; 90(6): 2207-2212

Physical Location	Centro Trasfusionale e di Talassemia Ospedale di Sciacca, Agrigento; Ospedale Pediatrico G. Di Cristina, Ospedale Villa Sofia, Ospedale V. Cervello, Palermo; Ospedale S. Elia, Caltanisetta ITALY
Participant characteristics	70 thalassaemics, 33 male & 37 female, 4-37, mean age 14.1 Excluded: advanced cirrhosis; positive HBsAg or anti-HIV; diabetes; autoimmune or metabolic liver disease; cardiomyopathy; non-organ-specific autoAb
HCV test methods	Viral detection: ELISA, RIBA (1&2 Ortho Diagnostics) & qualitative RT-PCR HCV Quantification: RT-PCR HCV Genotyping: type-specific primers and LiPA (Innogenetics)
Treatment	5MU recombinant IFN -2b (Intron-A, Schering Plough) thrice weekly for 2 months then 3MU thrice weekly for 10 months
Outcomes	Sustained response was normal ALT for at 36 months post IFN
Variables used in model	Cirrhosis; hepatic iron content.

Fernandez I, Castellano G, Domingo MJ et al. Scan J Gastroenterol 1997; 32(1): 70-6

Physical Location	Doce de Octubre Hospital, Madrid SPAIN
Participant characteristics	118 adults, 81 male & 37 female, mean age 43, chronic hepatitis Excluded: other liver disease; positive HBsAg or anti-HIV; diabetes
HCV test methods	Viral detection: 2nd generation ELISA (Ortho) & qualitative RT-PCR HCV Quantification: quantitative RT-PCR (Amplicor HCV monitor, Roche) HCV Genotyping: LiPA (Innogenetics)
Treatment	5MU IFN -2b (Intron A, Schering-Plough) thrice weekly for 12 months
Outcomes	Response was normal ALT at the end of therapy
Variables used in model	Age; necro-inflammation; fibrosis

Gavier B, Martinez-Gonzalez M, Riezu-Boj J et al. Gastroenterology 1997; 113: 1647-1653

Physical Location	Clinica Universitaria and Medical School, University of Navarra, Pamplona, SPAIN
Participant characteristics	181 adults, 128 male & 53 female, 18-71, mean age 44.1, mixed histology Excluded: other causes of chronic liver disease; decompensated cirrhosis; systemic illness; HIV; no serum available samples; alcohol <6 months prior to treatment
HCV test methods	Viral detection: 2nd generation ELISA & qualitative RT-PCR HCV Quantification: quantitative RT-PCR HCV Genotyping: type-specific RT-PCR
Treatment	3MU IFN daily for 2,3,4 months then 1.5-3MU thrice weekly up to total of 12 months
Outcomes	Sustained response was normal ALT (1-22 IU/L women and 1-29 IU/L men) and negative HCV RNA for at least 18 months
Variables used in model	Age; baseline serum AST, ALT, GGT; body weight; mode of transmission; ALT at 1st and 3rd month of treatment.

Hayashi J, Yasuhiro K, Kumiko U et al. Arch Internal Medicine 1998; 158(2): 177-181

Physical Location	Kyushu University Hospital, Fukuoka, JAPAN
Participant characteristics	311 adults, 199 male and 112 female, mixed histology Excluded: estrogen replacement; alcohol or drug abuse; homosexuality; positive HBsAg, anti-HIV
HCV test methods	Viral detection: ELISA (HCV EIA II, Abbott Laboratories) & qualitative RT-PCR HCV Quantification: competitive RT-PCR HCV Genotyping: C gene type-specific primers
Treatment	6MU human lymphoblastoid IFN (Sumiferon, Sumitomo Co) daily for 2 weeks then thrice weekly for 22 weeks
Outcomes	Sustained response was negative HCV RNA 6 months post IFN
Variables used in model	Age; sex; sex-age interaction.

Imai Y, Kawata S, Tamura S et al. Liver 1997; 17: 88-92

Physical Location	Osaka University Medical School, Ikeda Municipal Hospital, Hyogo Prefectural Nishinomiya Hospital, Kawanishi City Hospital, Ashiya Municipal Hospital, Osaka Central Hospital, Itami City Hospital, Toyonaka Municipal Hospital, Otemae Hospital, Izumisano Hospital, Osaka and Hyogo, JAPAN
Participant characteristics	84 adults, 62 male & 22 female, 18-70, mean age 52, mixed histology without cirrhosis Excluded: positive HBsAg; prior IFN; pregnancy; cirrhosis; other liver disease; autoimmune disease; other serious illness
HCV test methods	Viral detection: ELISA (HCV EIA II, Abbott Laboratories) & qualitative RT-PCR HCV Quantification: competitive RT-PCR HCV Genotyping: RT-PCR (no detail given)
Treatment	6MU recombinant IFN -2a daily for 2 weeks then: 1. 3MU thrice weekly for 22 weeks; 2. 6MU thrice weekly for 22 weeks
Outcomes	Sustained response was normal ALT and negative HCV RNA for at leat 6 months post IFN
Variables used in model	Age; sex; mode of infection; baseline serum ALT, platelet count; IFN schedule; Knodell score.

Jenkins PJ, Cromie SL, Bowden DS et al. MJA 1996; 164: 150-152

Physical Location	Alfred Hospital, Melbourne AUSTRALIA
Participant characteristics	58 adults, 34 male & 24 female, mean 39.6, mixed histology Excluded: not provided
HCV test methods	Viral detection: HCV Quantification: HCV Genotyping:
Treatment	3MU IFN thrice weekly (or more often) for at least 12 weeks
Outcomes	Sustained response was either normal ALT or negative HCV RNA six months post IFN
Variables used in model	Age, sex, risk factors, ALT, GGT, fibrosis, steatosis, necro-inflammation

Kikuchi I, Ueda A, Mihara K et al. Eur J Gastroent Hepatology 1998; 10: 859-863

Physical Location	Miyazaki Prefectural Hospital, JAPAN
Participant characteristics	67 adults, 84 male & 50 female, mean age 50, chronic hepatitis without cirrhosis Excluded: drug induced liver disease; alcoholism; HepB indications; autoimmune disease
HCV test methods	Viral detection: ELISA (C-100-3 antigen, Ortho Diagnostic Systems), 2nd generation ELISA (c100-3, c22-3, c200, Ortho Diagnostic Systems) & qualitative RT-PCR HCV Quantification: competitive RT-PCR HCV Genotyping: type-specific RT-PCR
Treatment	6MU human lymphoblastoid IFN (Sumiferon, Sumitomo Pharmaceutical Co) daily for 2 weeks then thrice weekly for 22 weeks
Outcomes	Sustained response was normal ALT levels for at least 6 months post IFN

Variables used in model	HLA alleles: HLA-B54; HLA-DR4; HLA-A24-B54-DR4.

Kumada T, Nakano S, Takeda I et al. J Gastroenterol Hepatology 1996; 11: 159-165

Physical Location	Ogaki Municipal Hospital, Ogaki-shi JAPAN
Participant characteristics	54 adults, 35 male & 19 female, 20-67, mean age 54.8, mixed histology Excluded: HepB; autoimmune hepatitis; primary biliary cirrhosis; alcoholic liver disease; Wilson's disease; drug-induced liver disease
HCV test methods	Viral detection: 2nd generation ELISA (Abbott Laboratories) & qualitative RT-PCR HCV Quantification: competitive RT-PCR HCV Genotyping: core region type-specific RT-PCR
Treatment	Human lymphoblast IFN (OPC18, Otsuka Pharmaceutical) at 5 or 10MU daily for 2 weeks then thrice weekly for 4 weeks, twice weekly for 20 weeks and once weekly for 12 weeks
Outcomes	Sustained response was normal ALT and negative HCV RNA 6 months post IFN
Variables used in model	Age; sex; baseline serum ALT; IFN schedule; Knodell score; duration of infection.

Le Guen B, Squadrito G, Nalpas B et al. Hepatol 1997; 25: 1250-1254

Physical Location	Hospital Necker, Paris FRANCE
Participant characteristics	95 adults, 54 male & 41 female, mean age 47, mixed Quantiplex histology Excluded: HepB; alcohol abuse
HCV test methods	HCV Quantification: bDNA (Quantiplex HCV RNA 2.0, Chiron) HCV Genotyping: core region type-specific RT-PCR & RFLP then PCR-SSCP
Treatment	Recombinant IFN 2b: 1. 3MU thrice weekly for 6 months; 2. 6MU thrice weekly for 6 months then 3MU for six months
Outcomes	Sustained response was normal ALT at least 24 weeks post IFN
Variables used in model	Genome complexity

Lin R, Liddle C, Byth K et al. J Viral Hepatitis 1996; 3: 85-96

Physical Location	Westmead Hospital, NSW AUSTRALIA
Participant characteristics	65 adults, 41 male & 24 female, mean age 46, mixed histology Excluded: other causes of liver disease; positive anti-HIV; pregnancy; serious medical or psychiatric illness; presence of leucopenia or thrombocytopenia
HCV test methods	Viral detection: 2nd generation ELISA (Ortho Diagnostics) & qualitative RT-PCR HCV Quantification: competitive RT-PCR HCV Genotyping: LiPA (Innogenetics)
Treatment	3MU IFN -2b thrice weekly for 6 months
Outcomes	Long term response was normal ALT 12 months post IFN and negative HCV RNA 6 months post IFN
Variables used in model	Age; sex; mode of infection; cirrhosis; duration of infection.

Magrin S, Craxi A, Fabiano C et al. J Hepatol 25: 583-590

Physical Location	Ospedale V. Cervello, Palermo ITALY
Participant characteristics	100 adults, 62 male & 38 female, mean age 47, mixed histology Excluded: positive HBsAg, anti-HIV, non-organ specific autoAb; blood transfusion; drug/alcohol abuse
HCV test methods	Viral detection: 2nd generation ELISA (Ortho Diagnostics) & qualitative RT-PCR HCV Quantification: competitive RT-PCR and bDNA HCV Genotyping: LiPA and sequencing
Treatment	10MU IFN□ -2b (Intron-A, Schering-Plough) thrice weekly for 2 months then 5MU thrice weekly for 4 months. Normal ALT stopped and others continued 5MU thrice weekly for 6 months
Outcomes	Sustained response was normal ALT 12 months post IFN
Variables used in model	Age; cirrhosis

Martinot-Peignoux M, Boyer N, Pouteau M et al. J Hepatol 1998; 29: 214-223

Physical Location	Hôpital Beaujon, Clichy FRANCE
Participant characteristics	296 adults, 185 male & 111 female, mean age 41, mixed histology Excluded: previous IFN therapy; pregnant or pregnancy risk; decompensated cirrhosis; depressive illness; positive anti-HIV or HBsAg; other causes of liver disease; prothrombin <50% normal; haemoglobin<11g/mL; neutrophil<$1.5x10^9$/L; platelet<$100x10^9$/L
HCV test methods	Viral detection: 3rd generation ELISA and RIBA (Ortho Diagnostics) plus qualitative PCR (AMPLICOR HCV Amplification Kit, Roche Diagnostics) HCV Quantification: bDNA signal amplification (HCV RNA 2.0, Chiron Diagnostics) HCV Genotyping: LiPA (InGeN, Rungis)
Treatment	IFN□ -2a (Roferon, Hoffman-LaRoche), IFN□ -2b (IntronA, Schering-Plough) or lymphoblastoid IFN□ (Wellferon, Wellcome): 1. 3MU thrice weekly for 3 months; 2. 3MU thrice weekly for 6 months; 3. 3MU thrice weekly for 12 months or 5MU thrice weekly for 6 or 12 months; 4. 3MU-10MU thrice weekly for 6 months
Outcomes	Sustained response was normal ALT and negative HCV RNA 6 months post IFN
Variables used in model	Age; baseline serum ALT; IFN schedule; mode of infection.

Martinot-Peignoux M, Marcellin P, Pouteau M et al. Hepatology 1995; 22: 1050-1056

Physical Location	Hôpital Beaujon, Clichy FRANCE
Participant characteristics	141 adults, 79 male & 62 female, mean age 42, mixed histology Excluded: previous IFN therapy; pregnant or pregnancy risk; decompensated cirrhosis; depressive illness; positive anti-HIV or HBsAg; other causes of liver disease; prothrombin <50% normal; haemoglobin<11g/mL; neutrophil<$1.5x10^9$/L; platelet<$100x10^9$/L

HCV test methods	Viral detection: 2nd generation ELISA and RIBA (Ortho Diagnostic Systems) HCV Quantification: bDNA signal amplification (Quantiplex HCV RNA 2.0, Chiron Diagnostics) HCV Genotyping: LiPA (InGeN, Rungis)
Treatment	IFN -2b (IntronA, Schering-Plough): 1. 3MU thrice weekly for 24 weeks; 2. 3MU-5MU-10MU thrice weekly for 24 weeks. Lymphoblastoid IFN (Wellferon, Wellcome): 1. 3MU thrice weekly for 24 weeks; 2. 3MU thrice weekly for 48 weeks; 3. 5MU thrice weekly for 24 weeks; 4. 5MU thrice weekly for 48 weeks.
Outcomes	Sustained response was normal ALT 6 months post IFN
Variables used in model	Age; sex; mode of infection; baseline serum ALT; cirrhosis; IFN schedule; duration of infection.

Matsumoto A, Tanaka E, Suzuki T et al. Dig Dis Sci; 1994: 39(6): 1273-1280

Physical Location	Shinshu University Hospital, Matsumoto Japan
Participant characteristics	36 adults, 25 male & 11 female, 24-62, mean age 47.6, mixed histology Excluded: antiviral or immunosuppressive therapy prior 6 months; positive autoAb; pregnancy; depression; serious medical illness; leucopenia; thrombocytopenia
HCV test methods	Viral detection: 2nd generation ELISA (Abbott Laboratories) and qualitative RT-PCR HCV Quantification: competitive RT-PCR HCV Genotyping: type-specific RT-PCR
Treatment	IFN -2a (Roche): 1. 3MU daily for 4 weeks; 2. 3MU daily for 2 weeks then thrice weekly for 24 weeks; 3. 9MU daily for 2 weeks then thrice weekly for 24 weeks
Outcomes	Responders had normal ALT for 24 weeks post IFN
Variables used in model	Age; sex; mode of infection; baseline serum ALT; IFN schedule; Knodell score.

Nomura H, Tsuchiya Y, Kimura Y et al. Fukuoka Acta Med 1997; 88(6): 253-260

Physical Location	Shin-Kokura Hospital, Kita-Kyushu Medical Center, Kita-Kyushu Municipal Tobata Hospital, Hara Doi Hospital JAPAN
Participant characteristics	50 adults, 33 male & 17 female, 28-65, mean age 49.8, mixed histology - unstaged Excluded: positive HBsAg
HCV test methods	Viral detection: 2nd generation ELISA (Ortho Diagnostics) & qualitative RT-PCR HCV Quantification: bDNA signal amplification (Quantiplex HCV RNA, Chiron) HCV Genotyping: RT-PCR and sequencing
Treatment	6MU human lymphoblast IFN (Sumiferon, Sumitomo Pharmaceutical Co) daily for 4 weeks then thrice weekly for 20 weeks
Outcomes	Complete responder was normal ALT (<30 IU/L) and negative HCV RNA 6 months post IFN
Variables used in model	Age; sex; liver histology.

Papatheodoridis GV, Katsouldou A, Touloumi G et al Eur J Gastroent Hepatol 1996; 8: 469-475

Physical Location	Western Attica General Hospital, Athens GREECE
Participant characteristics	60 adults, 42 male & 18 female, 24-80, mean age 42.7, mixed histology Excluded: decompensated liver disease; other causes of liver disease; antiviral therapy prior 6 months; psychosis or depression; drug abuse; positive HBsAg or HIV; renal insufficiency; multi-transfused or haemophilia patients
HCV test methods	Viral detection: 2nd generation ELISA (Abbott Laboratories), RIBA (RIBA-2, Chiron) & qualitative RT-PCR HCV Quantification: HCV genotype quantification (Amplicor HCV, Roche) HCV Genotyping: LiPA (INNO-LIPA HCV, Innogenetics)
Treatment	3MU INF□ -2b (Intron-A, Schering-Plough) thrice weekly for 6 months or 12 months
Outcomes	Sustained response if ALT normal at least 6 months post IFN
Variables used in model	Cirrhosis; IFN schedule

Pawlotsky J, Roudot-Thoraval F, Bastie A et al. J Infect Dis 1996;174: 1-7

Physical Location	Hopital Henri Mondor, Creteil FRANCE
Participant characteristics	113 adults, 75 male & 38 women, 18-74, mean age 46.2, mixed histology Excluded: <18 or >75; decompensated liver; hepatocellular carcinoma; pregnancy; depression; positive HBsAg or HIV; drug addiction; alcohol abuse; autoimmune disease; albumin <30g/L; prothrombin time <50% of controls; bilirubin >60□ mol/L; platelet <70,000g/L; neutrophil <1500g/L; haemoglobin <11g/L; serum creatinine >120□ mol/L; antiviral or immunomodulatory therapy
HCV test methods	Viral detection: ELISA, RIBA (Ortho Diagnostics), qualitative RT-PCR and HCV IgM ELISA test (Abbott Diagnostica) HCV Quantification: bDNA (Quantiplex HCV RNA 2.0, Chiron) HCV Genotyping: LiPA (Inno-LiPA, Innogenetics)
Treatment	3MU IFN□ -2a (Roferon, Roche) thrice weekly for at least 3 months, then if normal ALT 3MU thrice weekly for 3 months
Outcomes	Sustained response was normal ALT and negative HCV RNA 12 months post IFN
Variables used in model	Age; sex; baseline serum GGT; body weight; anti-core IGM antibodies

Patlowsky J, Pellerin M, Bouvier M et al. J Med Virol 1998; 54: 256-264

Physical Location	Hopital Henri Mondor, Creteil FRANCE
Participant characteristics	114 adults, 76 male & 38 female, 18-74, mean age 46.2, mixed histology Excluded: <18 or >75; decompensated liver; hepatocellular carcinoma; pregnancy; depression; positive HBsAg or HIV; drug addiction; alcohol abuse; autoimmune disease; albuminaemia <30g/L; prothrombin time <50% of controls; bilirubin >60□ mol/L; platelet <70,000g/L; neutrophil <1500g/L; haemoglobin <11g/L; serum creatinine >120□ mol/L; antiviral or immunomodulatory therapy

HCV test methods	Viral detection: qualitative RT-PCR HCV Quantification: bDNA (Quantiplex HCV RNA 2.0, Chiron) HCV Genotyping: LiPA (Inno-LiPA, Innogenetics) and RT-PCR SSCP
Treatment	3MU IFN□ -2a (Roferon, Roche) thrice weekly for at least 3 months, then if normal ALT 3MU thrice weekly for 3 months
Outcomes	Sustained response was normal ALT and negative HCV RNA 12 months post IFN
Variables used in model	Anti-core IGM antibodies; genetic complexity of HVR1 major variants

Rumi M, Del Ninno E, Parracicini ML et al. Hepatol 1996; 24: 1366-1370

Physical Location	Policlinic Hospital, Milan ITALY
Participant characteristics	234 adults, 159 male & 75 female, mean age 48, mixed histology Excluded: positive HBsAg, anti-HIV, anti-organ specific autoAb; abnormal antitrypsin, copper, iron, transferrin concentrations and thyroid function; drug and alcohol induced liver disease; pregnancy; jaundice; ascites; encephalopathy; upper GI haemorrhage; thrombocytopenia; leucopenia
HCV test methods	Viral detection: ELISA (Ortho Diagnostic) and qualitative RT-PCR HCV Quantification: bDNA (Quantiplex HCV RNA 2.0, Chiron) HCV Genotyping: LiPA (Inno-LiPA, Innogenetics)
Treatment	IFN□ -2a (Roferon-A, Hoffman-La Roche) or IFNa-N1 (Wellferon, Wellcome Laboratories): 6MU thrice weekly until ALT/AST normal for 4 weeks then 3MU thrice weekly to total of 12 months treatment
Outcomes	Sustained response if ALT/AST and negative HCV RNA 12 months post IFN
Variables used in model	Age; sex; mode of infection; baseline serum ALT; cirrhosis; duration of infection; serum IFN-neutralising antibodies.

Sartori M, Andorno S, Avagadro E et al. Ital J Gastroenterol 1996; 28: 452-456

Physical Location	Ospedale Maggiore, Novara ITALY
Participant characteristics	90 adults, 51 male & 39 female, 20-87, mean age 58, mixed histology – with cirrhosis Excluded: hepatocellular carcinoma; no biopsy report; contraindications to IFN; positive HBsAg
HCV test methods	Viral detection: ELISA and RIBA (Ortho Diagnostic System) & qualitative PCR (DEIA, Sorin Biomedica) HCV Genotyping: LiPA (INNO-LIPA HCV, Innogenetics)
Treatment	3MU INF□ thrice weekly for at least 6 months
Outcomes	Sustained response if ALT normal at least 6 months post IFN
Variables used in model	Age; sex; type of liver disease

Shiratori Y, Kato N, Yokosuka O et al. Gastroenterology 1997; 113: 558-566 (Tokyo-Chiba Hepatitis Research Group)

Physical Location	16 participating hospitals and universities, Tokyo & Chiba, JAPAN
Participant characteristics	272 adults, 189 male & 83 female, 23-65, mean age 50.2, mixed histology – non cirrhotic Excluded: liver cirrhosis or other liver disease eg. HepB, autoimmune hepatitis, primary biliary cirrhosis, drug-induced liver disease

HCV test methods	HCV Quantification: RT-PCR (Amplicor-HCV monitor assay) & bDNA probe assay (v1, Chiron) HCV Genotyping: serotyping assay (SRL laboratory Co)
Treatment	Natural IFN□ (Sumitomo Pharmaceutical Co): 1. 6MU thrice weekly for 6 months; 2. 9MU thrice weekly for 6 months
Outcomes	Response was negative HCV RNA 12 months post IFN
Variables used in model	Age; IFN schedule.

Soriano V, Garcia-Samaniego J, Bravo R et al. Clinical Infectious Diseases 1996; 23: 585-591 (Hepatitis-HIV Spanish Study Group)

Physical Location	10 participating hospitals and universities, SPAIN
Participant characteristics	119 adults, 81 male & 26 female, mean age 30.8, co-infection with HIV Excluded: positive HBsAg; alcohol >60g/d; autoimmune disease; metabolic disease; drug use
HCV test methods	Viral detection: 2nd generation ELISA and RIBA (Chiron RIBA HCV test, Ortho Diagnostics) HCV Quantification: bDNA (Quantiplex HCV RNA, Chiron) HCV Genotyping: LiPA (inno-LiPa, Innogenetics)
Treatment	5MU IFN□ thrice weekly for 3 months then 3MU thrice weekly for 9 months
Outcomes	Sustained response was normal ALT and negative HCV RNA post IFN
Variables used in model	Sex; CD4 absolute count; CD4 percentage.

Toyoda H, Kumada T, Nakano S et al. J Hepatol 1997; 26: 6-13

Physical Location	Ogaki Municipal Hospital, Ogaki JAPAN
Participant characteristics	62 adults, 42 male and 20 female, 22-64, mean age 49.1, mixed histology Excluded: decompensated liver disease; serious medical illness; positive HBsAg, HBV DNA, anti-HIV-1, non-organ-specific autoAb
HCV test methods	Viral detection: qualitative RT-PCR HCV Quantification: bDNA HCV Genotyping: type-specific RT-PCR & single-strand conformation polymorphism
Treatment	600 megaU lymphoblastoid IFN□□ (Sumiferon, Sumitomo Pharmaceutical) daily for 2 weeks then thrice weekly for 22 weeks
Outcomes	Long-term response was negative HCV RNA 6 months post IFN and normalised ALT 48 weeks post IFN
Variables used in model	Age: sex; baseline serum ALT ; liver histology; quasispecies.

Toyoda H, Nakano S, Kumada T et al. Am J Gastroenterol 1996; 91(4): 743-747

Physical Location	Ogaki Municipal Hospital, Ogaki JAPAN
Participant characteristics	63 adults, 41 male & 22 female, 22– 64, mean age 49.4, mixed histology Excluded: decompensated liver disease; serious medical illness; positive HBsAg, HBV DNA, anti-HIV-1, non-organ-specific autoAb
HCV test methods	Viral detection: 2nd generation serology assay & qualitative RT-PCR HCV Quantification: competitive RT-PCR & bDNA HCV Genotyping: type-specific RT-PCR

Treatment	6MU natural IFN□ □ (Sumiferon, Sumitomo Pharmaceutical): 1. daily for 2 weeks then thrice weekly for 22 weeks; 2. daily for 8 weeks then twice weekly for 12 weeks
Outcomes	Sustained response was normal ALT and negative HCV RNA for 68 – 72 weeks post IFN
Variables used in model	Age; sex; baseline serum ALT; IFN schedule; liver histology

Tsubota A, Kumada H, Chayama K et al. Dig Dis Sci 1996; 41 (10): 1925-1932

Physical Location	Toranomon Branch Hospital and Mishuku Hospital, Tokyo JAPAN
Participant characteristics	185 adults, 55 male & 130 female, mean age 48.2, mixed histology Excluded: other forms of liver disease; coexistence of serious medical illness; IFN, antiviral or immunomodulant therapy prior year; positive HBsAg or HBcAb; pregnancy/ lactation
HCV test methods	Viral detection: qualitative RT-PCR HCV Quantification: bDNA (Chiron) HCV Genotyping: NS5 type-specific primers & serotyping using ELISA (International Reagents Corp)
Treatment	Human lymphoblastoid IFNα (Sumitomo Pharmaceuticals) 6MU daily for 8 weeks the twice weekly for 16 weeks
Outcomes	Sustained response if ALT concentration normal for at least 6 months post IFN therapy
Variables used in model	Knodell score

Tsubota A, Chayama K, Arase Y et al. J Gastroenterol Hepatol 1993; 8: 535-539

Physical Location	Toranomon Branch Hospital, Tokyo JAPAN
Participant characteristics	149 adults, 113 male & 36 female, 19–71, mean age 46, mixed histology Excluded: other forms of liver disease; coexistence of systematic illness; positive HBsAg, anti-HBc
HCV test methods	Viral detection: ELISA (Ortho Diagnostic Systems) & qualitative RT-PCR HCV Genotyping: NS5 type-specific primers
Treatment	Either human lymphoblastoid IFNα (Sumitomo Pharmaceuticals) or IFNβ (Toray Industries): 1. 6MU twice weekly for 24 weeks; 2. 6MU daily for 8 weeks; 3. 6MU daily for 8 weeks then twice weekly 16 weeks
Outcomes	Sustained response if ALT concentration normal for at least 6 months post IFN therapy
Variables used in model	IFN schedule; liver histology

Appendix D Studies excluded from the review

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Appendix E Study results addressing review Question 1

Question 1: Does pretreatment determination of HCV genotype predict response to interferon therapy in patients with hepatitis C?

Table 5 Genotyping - Odds Ratios associated with sustained response

Reference	Number of patients	Geno-type (reference)	Odds Ratio	Confidence Interval	P-value
Ascione (1998)	80	Not reported	-	-	NS
Shiratori (a) (1997) using assay #1	272	2 (1)	4.29	2.01-9.16	0.0002
Shiratori (b) (1997) using assay #2	272	2 (1)	7.31	2.93-18.22	0.0001
Tsubota (1996)	185	2 (1)	6.96	3.10-15.61	<0.0001
Papatheodoridis (1996)	60	2/3 (1)	1.34	1.02-1.76	0.04
Martinot-Peignoux (a) (1998)	228	1a (1b)	0.63	0.10-4	<0.001
Arase (1994)	38	2a (1b)	-	-	NS
Hayashi (a) (1998)	311	2a (1b)	6.2	2.94-13.08	<0.001
Martinot-Peignoux (b) (1998)	228	2a (1b)	12.4	3.5-44.8	<0.001
Matsumoto (1994)	36	2a/2b (1b)	1.65	1.29-2.11	0.0004
Hayashi (b) (1998)	311	2b (1b)	3.04	1.19-7.75	<0.001
Brouwer (a) (1998)	336	2 (1b)	20	5.4-77	<0.001
Brouwer (b) (1998)	336	3 (1b)	9.4	2.7-33	<0.001
Martinot-Peignoux (c) (1998)	228	3a (1b)	6.5	2.2-19.5	<0.001
Martinot-Peignoux (a) (1995)	141	3a (1b)	33.6	4.4-260	<0.05
Brouwer (c) (1998)	336	4 (1b)	5.0	0.9-29	NS
Brouwer (d) (1998)	336	Not 1b (1b)	2.5	0.4-15	NS
Di Marco (1997ii)	67	Not 1b (1b)	4.46	1.24-16.0	-
Martinot-Peignoux (b) (1995)	141	Not 1b/3a (1b)	10	1.4-68.7	<0.05
Chayama (1996)	38	1b/2a (2b)	15.04	1.43-1,157.75	0.028

Table 5 continued Genotyping - Odds Ratios associated with sustained response

Reference	Number of patients	Geno-type (reference)	Odds Ratio	Confidence Interval	P-value
Chemello (a) (1995i)	174	1b (1a/2b/4)	-	-	NS
Chemello (b) (1995i)	174	2a (1a/2b/4)	5.4	1.88-15.52	0.0017
Chemello (c) (1995i)	174	3 (1a/2b/4)	6.62	1.71-9.43	0.0083
Chemello (a) (1995ii)	321	2 (2/3)	4.31	1.97-162.38	0.0004
Chemello (b) (1995ii)	321	3 (not 2/3)	10.7	3.30-34.67	0.0001
Chemello (1997)	92	2 (not 2/3)	-	-	NS
Gavier (1997)	181	3 (not 3)	6.27	2.21-17.9	<0.001
Kumada (1996)	54	Not 2a (2)	0.09	0.02-0.41	0.0015
Nomura (1997)	50	1b (2a/2b)	0.49	0.09-2.65	0.404
Toyoda (1996) Assay #1	63	1b (2a/2b)	0.16	0.04-0.72	0.02295
Toyoda (1996) Assay #2	63	1b (2a/2b)	0.49	0.10-2.34	0.37870
Tsubota (1993)	149	2a (2b)	0.23	0.10-0.53	0.0008

Table 6 Genotyping - Odds Ratios associated with end of treatment response

Reference	Number of patients	Geno-type (reference)	Odds Ratio	Confidence Interval	P-value
Di Marco (1997i)	310	1 (not 1)	3.32	0.91-12.1	0.06
Toyoda (1997)	62	1b (2a/2b)	0.95	0.21-4.28	0.50711
Sartori (1996)	31	2a (1b)	24.0	2.19-261	-
Fernández (1997)	51	Not 1b (1b)	5.4	0.97-30	-

Table 7 Genotyping - Odds Ratios associated with end of treatment relapse

Reference	Number of patients	Geno-type (reference)	Odds Ratio	Confidence Interval	P-value
Chemello (1995ii)	321	1 (not 1)	2.05	1.10-3.85	0.0273

Table 8 Genotyping - Odds Ratios associated with no response

Reference	Number of patients	Geno-type (reference)	Odds Ratio	Confidence Interval	P-value
Kikuchi (1998)	67	2a/2b (1b)	2.14	2.27-10.28	0.35
Chemello (a) (1995ii)	321	2 (not 2/3)	-	-	NS
Chemello (b) (1995ii)	321	3 (not 2/3)	-	-	NS
Rumi (a) (1996)	234	1a (2a/2c)	13.45	1.56-11.6	-
Rumi (b) (1996)	234	1b (2a/2c)	3.11	1.38-6.99	-
Rumi (c) (1996)	234	3a (2a/2c)	4.87	1.16-20.42	-
Le Guen (1997)	95	1a/1b (not 1)	7.48	1.73-32.3	-
Pawlotsky (1996)	113	1a/1b (not 1)	3.6	1.4-9.2	<0.009

Appendix F Study results addressing review Question 2

Question 2: Does pretreatment determination of viral load predict response to interferon therapy in patients with hepatitis C?

Table 9 Viral load - Odds Ratios associated with sustained response

Reference:	Number of patients	Viral level (reference)	Odds Ratio	Confidence Interval	P-value
Brouwer (a) (1998)	336	High (lowest category)	0.2	0.0-0.6	<0.01
Brouwer (b) (1998)	336	Highest (lowest category)	0.1	0.0-0.3	<0.001
Hayashi (1998)	311	High (lowest category)	0.1	0.05-0.2	<0.001
Imai (1997)	84	High (lowest category)	0.89	0.83-0.96	0.0035
Kumada (1996)	54	High (lowest category)	0.62	0.44-0.87	0.0061
Matsumoto (1994)	36	High (lowest category)	0.94	0.87-1.02	0.1965
Nomura (1997)	50	High (lowest category)	0.08	0.01-0.48	<0.01
Chayama (1997)	110	Low (highest category)	5.68	1.93-16.71	0.002
Chayama (1996)	38	Low (highest category)	35.02	3.012-392.29	0.006
Lin (1996)	65	Low (highest category)	11.3	1.4-92.1	0.02
Magrin (1996)	100	Low (highest category	4.39	1.2-16.0	0.0174
Martinot-Peignoux (a) (1998)	228	Low (highest category)	4.5	1.4-15	< 0.001
Martinot-Peignoux (b) (1998)	228	Lowest category (highest category)	20.5	5.1-83.2	<0.001
Martinot-Peignoux (a) (1995)	141	Low category (highest category)	3.4	0.6-18.6	<0.05
Martinot-Peignoux (b) (1995)	141	Lowest category (highest category)	24.7	3.7-164	<0.05
Pawlotsky (1998)	101	Low (highest category)	1.26	-	<0.04
Shiratori (a) (1997) using assay #1	272	Low (highest category)	6.99	3.47-14.08	0.0001
Shiratori (b) (1997) using assay #2	272	Low (highest category)	16.13	6.41-40.00	0.0001
Soriano (1996)	53	Low (highest category)	4.22	1.16-15.36	0.0290
Toyoda (1996) Assay #1	63	Low (highest category)	25.21	3.34-190.18	0.00284
Toyoda (1996) Assay #2	63	Low (highest category)	40.08	1.45-1108.92	0.00264
Tsubota (1996)	185	Low (highest category)	2.12	1.04-4.36	0.041

Table 10 Viral load - Odds Ratios associated with end of treatment response

Reference:	Number of patients	Viral level (reference)	Odds Ratio	Confidence Interval	P-value
Toyoda (1997)	62	Low (highest category)	4.0	0.77-20.83	0.1515
Magrin (1996)	100	Low (highest category	3.45	1.1-10.8	0.0329

Table 11 Viral load - Odds Ratios associated with no response

Reference	Number of patients	Viral level (reference)	Odds Ratio	Confidence Interval	P-value
Le Guen (1997)	95	High (lowest category)	11.6	1.43-93.5	-
Rumi (a) (1996)	234	High (lowest category)	4.8	1.86-11.76	-
Rumi (b) (1996)	234	Highest (lowest category)	6.48	2.57-16.36	-
Kikuchi (1998)	67	Low (highest category)	27.38	5.36-139.7	0.0002

Appendix G Study results addressing review Question 3

Question 3: Is detection of viraemia by qualitative PCR during antiviral therapy predictive of a sustained virological response in patients with hepatitis C

Table 12 RNA detection test - Odds Ratios associated with sustained response

Reference	Number of patients	Time of test	Odds Ratio	Confidence Interval	P-value
Arase (1994)	38	1 month	29.81	3.01- 294.72	0.175
Di Marco (1997i)	310	End of treatment	30.1	3.3-273	0.001
Gavier (1997)	181	1 month	19.5	4.94-77.2	<0.001

Abbreviations

bDNA	branched DNA
ELISA	enzyme linked immunoabsorbent assay
HCV	hepatitis C
HSD	highly specialised drugs
IgG	immunoglobulin G
LiPA	line probe assay
PCR	polymerase chain reaction
RFLP	restriction fragment length polymorphism
RIBA	recombinant immunoblot assay
RNA	ribonucleic acid
RT-PCR	reverse transcriptase and polymerase chain reaction

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