Clinical guidelines on the management of hepatitis C

Compiled on behalf of the Royal College of Physicians of London and the British Society of Gastroenterology
by
J C L Booth, J O'Grady, J Neuberger

Summary of recommendations

Patients infected with hepatitis C virus (HCV) should be referred to a clinician with a particular interest in the infection. Patients must have access to adequate counselling from a health carer with knowledge and experience of chronic HCV infection. All patients must have access to the appropriate diagnostic and therapeutic options available in the management of HCV infection.

Where possible a judgement is made on the quality of information used to generate the guidelines. Categories of evidence are classified:

A - randomised control trials (RCT's), meta-analyses or systematic reviews
B - prospective, retrospective or cross-sectional studies
C - expert opinion

Guideline recommendations

Diagnosis

- Patients with suspected HCV infection should be tested for anti-HCV by an up-to-date (currently third generation) ELISA test (C).
- All patients with positive antibody tests and those patients thought to be at risk of HCV infection despite negative or indeterminate serological tests should undergo PCR testing of the serum. A positive result confirms current viraemia whereas a negative test suggests non-viraemic infection, transient absence of viraemia or recovered infection, a level of viraemia below the detection limit of the assay or may reflect a non-specific ELISA result (B).
- Patients with positive ELISA but negative PCR should therefore be tested with recombinant immunoblot assay to confirm antibody status (B).
- A qualitative PCR test is recommended in immunodeficient patients with suspected HCV infection (B).
- The results of routine liver tests correlate poorly with both necro-inflammatory and fibrosis scores found on liver biopsy (B).
- Liver biopsy is valuable for assessing status of liver inflammation, potential progression of fibrosis and the presence or absence of cirrhosis. To clarify these, and to assess suitability for treatment, liver biopsy is recommended for patients found to be viraemic, whether or not liver function tests are abnormal. Standard histological scoring systems by a suitably experienced pathologist, should be used to encourage uniformity of histological reports. The risks and benefits of liver biopsies must be fully discussed with the patient (B).
- The measurement of HCV RNA concentrations in serum and the determination of HCV genotype are recommended and should be used to determine the duration of treatment (see later) (A).

Counselling regarding transmission

- Patients should be counselled on the implications of HCV positivity and advised on the risks of

infectivity.

- the natural history is slowly progressive (median time to cirrhosis = 28-32 years) (A).
- HCV positive patients should not donate blood, organs, tissues or semen (C).
- the risk of sexual transmission is small - maximum of 5%, but possibly much less (B). There is insufficient evidence firmly to recommend barrier contraception in stable monogamous relationships but is strongly advised for HCV infected patients with multiple sexual partners (C).
- transmission from mother to child is rare - maximum of 6%, but transmission rates are higher in HIV positive mothers (B).
- breast feeding is not contraindicated (C).
- household contacts should avoid third party contact with blood by not sharing toothbrushes and razors, and by covering open wounds (C).
- standard precautions for the prevention of transmission to medical personnel and patients is mandatory in health care settings (C).
- needle exchange programs in drug addicts may help reduce parenterally transmitted infection (C).

- Current IVDUs should not be treated although in selected cases ex-IVDUs taking regular oral methadone may be considered for treatment (C).

Treatment - General measures

- Patients should be advised that excess alcohol consumption (50 g/day) appears to hasten the progression of disease (B).
- Consideration should be given to entering patients with established cirrhosis into surveillance programmes for hepatocellular cancer, if their general state of health is sufficiently good that emerging cancers could be appropriately treated (C).
- Patients must be screened for their suitability to receive Interferon and Ribavirin, with criteria which includes proven viraemia and abnormal liver histology (C).
- Interferon (IFN) and Ribavirin are currently the only licensed treatments for HCV in the United Kingdom.
- IFN/Ribavirin combination is the treatment of choice for IFN naive patients (A).
- IFN/Ribavirin combination is also recommended for those patients relapsing after IFN monotherapy (A).
- IFN monotherapy should be considered for those patients in whom ribavirin is contraindicated (C).

Treatment - Interferon monotherapy

- We recommend IFN monotherapy should be initiated at a dose of 3MU three times per week by injection (B).
- IFN monotherapy should be continued for 12 months unless there is evidence of failure to respond (see below) (B).
- There is no evidence to suggest that one type of ?-interferon is superior to another (alfa-2b, alfa-2a, alfa-n1 and consensus interferon (CIFN) (B).

Treatment - Interferon/Ribavirin combination therapy

- Recent results of large randomised controlled studies have shown improved response rates for IFN/Ribavirin combination therapy in IFN naive and relapsers when compared to IFN monotherapy (A).

- Combination therapy consists of IFN at standard doses (usually 3MU three times per week) with Ribavirin 1000mg/day for patients weighing 75kg or less and 1200mg for those weighing more than 75kg. (A)

- In viraemic patients, the decision to offer treatment should be influenced by the histological findings (B):

    - treatment can be reasonably withheld in patients with mild disease (see text) but they should be followed to see if there is evidence of progressive liver disease by the use of repeated biopsy after an interval (C).

    - treatment should be offered to those patients shown to have moderate disease (C).

    - cirrhotic patients respond less well to IFN monotherapy but sustained responses have improved with IFN/Ribavirin combination treatment. There is no conclusive evidence that treatment in this group of patients delays progression of liver disease or the development of hepatocellular carcinoma (B).

- Treatment should not be withheld on the basis of genotype analysis or the measurement of HCV RNA levels (B).

- The duration of combination depends of the genotype and level of viraemia (A).

- Patients infected with non-HCV 1 (mostly genotype 2 or 3) should be treated for 6 months irrespective of the level of viraemia (A).

- Patients infected with genotype 1 and low level viraemia (< 2 million copies per ml) should be treated for 6 months whereas 12 months treatment is recommended for those infected with genotype 1 and high level viraemia (2 million copies per ml) (A). If HCV quantitation is not available treatment is recommended for 12 months in HCV 1 infected patients (A).

- Patients unlikely to respond to IFN monotherapy can be identified at 3 months by persistent elevation of serum transaminase levels and the persisting presence of HCV RNA by PCR in serum (B).

- If ALT levels are normal or HCV RNA negative (or both) at 3 months, treatment should be continued for the full duration (12 months) (B). In patients with initially normal ALT levels, failure to become RNA negative at 3 months suggests longer treatment will be ineffective (B).

- The recommendation that early treatment response can be used to predict sustained response does not apply to patients receiving combination therapy (A). In those patients receiving 12 months IFN/Ribavirin combination therapy a positive PCR at 6 months is an indication to stop treatment (C).

- Although transient or mild side-effects are common during IFN monotherapy, serious toxicity requiring reduction in dose or cessation of treatment occurs in 5-10% of patients during treatment (A).

- Withdrawal from IFN/Ribavirin combination therapy occurs more often with 10-20% of patients requiring a reduction in dose or cessation of combination therapy (A).

- Patients with a combined biochemical and virological response at the end of IFN monotherapy, who relapse in follow-up over the next year, have a significant chance of a sustained response after further treatment with IFN/Ribavirin (A).

- Patients with a biochemical but not virological response during initial treatment with IFN

monotherapy are unlikely to have a sustained response to further treatment with IFN/Ribavirin (A).

- There is continuing development in the treatment of patients with HCV infection. The guidelines will need regular and frequent review (C).

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Contents

1.0 Guidelines

1.1 The need for guidelines

1.1.1 Hepatitis C virus (HCV) is a major health care concern in the United Kingdom affecting some 200,000 to 400,000 individuals. The majority of these patients will have

chronic HCV infection and many will develop chronic liver disease with the risk of developing cirrhosis and hepatocellular carcinoma (HCC). Successful treatment will arrest the progression of liver disease and so prevent the serious complications of chronic HCV infection. In addition, treatment will reduce the numbers of HCV infected individuals.

1.1.2 The relatively high cost of treatment enforces the need for a systematic approach for this condition so that resources are used most effectively. The development of clinical guidelines is important, as these will assist purchasing authorities, providers, clinicians, primary care groups and patients in making decisions about appropriate treatment.

1.2 The development of guidelines

Rigour of development/systematic critical review of literature

Guideline development group

1.2.1 The development of these clinical guidelines follows a workshop held at the Royal College of Physicians on 3 December 1997. This meeting was jointly co-ordinated by the NHS Executive, The Royal College of Physicians, the British Society of Gastroenterology, British Liver Trust and the British Association for the study of the Liver (BASL). The workshop was attended by Hepatologists, Gastroenterologists, Histopathologists, Virologists, General Practitioners, Clinical Nurse Specialists, patient representatives, health care economists and NHS managers. Attendants were chosen to represent key professional disciplines and interest groups likely to be affected by the guidelines. The literature was reviewed by a clinician attending the workshop and the guidelines written under the guidance of a steering committee, which met regularly during the development process. The document was circulated to both clinicians (including gastroenterologists and hepatologists) and non-clinicians for comments before the final guidelines were drawn up - see Appendix 1. The guidelines were presented at the 1999 BASL meeting in London where consensus was achieved on some of the more controversial issues.

Strategy

1.2.2 The literature was searched comprehensively so as to include the most up to date literature. Literature searched included results of randomised control trials (RCT's), meta-analyses, prospective and retrospective studies and in some instances from evidence obtained from expert committee reports or opinions.Where possible a judgement is made on the quality of information used to generate the guidelines. Categories of evidence are classified:

A - randomised control trials (RCT's), meta-analyses or systematic reviews
B - prospective, retrospective or cross-sectional studies
C - expert opinion

1.2.3 The final version of the guidelines represents the views of the steering committee and all areas of disagreement, or where there is a lack of convincing evidence, have been made explicit in the text. It is anticipated that the guidelines will be regularly updated, perhaps on a yearly basis, to allow new developments to be quickly incorporated into the management strategy.

Context and Content

1.2.4 The guidelines are intended to improve the patient's management from first diagnosis to completion of a course of antiviral therapy and during follow-up. Patient preferences must be sought and decisions made jointly by patient and health carer based on the risks and benefits of any therapeutic intervention.

1.2.5 An assessment of the costs of instituting the guidelines must be made. It should be stressed that the costs are "front-loaded" and that by preventing disease progression these costs will be offset not only by improved health but also by reducing overall health costs by preventing disease progression.

Application and presentation

1.2.6 The national guidelines will be used as a framework for local groups to develop according to local needs.

1.2.7 The resource implications include the high costs for interferon (IFN) and Ribavirin treatment and for regular outpatient visits including the diagnostic and monitoring blood tests.

Statement of Intent

1.2.8 The guidelines should not be regarded as the standard for medical care for all patients. Individual cases must be managed on the basis of all clinical data available for that case and are subject to change as scientific knowledge advances.

2.0 Background

2.1 Epidemiology

Prevalence

2.1.1 Since the discovery of HCV and the development of diagnostic tests, almost all of the non-A non-B (NANB) post transfusion hepatitis cases have been shown to be due to HCV infection [1-7]. HCV has been encountered worldwide with WHO estimates of 170 million infected patients worldwide, and up to 90% of these will progress to chronic liver disease [8]. In total 130 countries worldwide have reported HCV infection.

2.1.2 The prevalence rates of infection in healthy blood donors ranging from 0.01-0.02% in the UK and Northern Europe [9], 1-1.5% in Southern Europe 3 to rates of 6.5% in parts of equatorial Africa [10]. Prevalence rates as high as 20% have been found in Egypt [11] [12]. Surveillance of HCV in England and Wales has been carried out by the Public Health Laboratory Service Communicable Disease Surveillance Centre since 1990. Estimates suggest that between 200,000 to 400,000 individuals are infected with the virus in the UK, although the true number remain unknown.

2.1.3 Between 1992 and 1996 a total of 5,232 reports of confirmed HCV infection have been received from laboratories in England and Wales (Ramsey 1997). Most were in the 25-34 year age group (38%) and the 35-44 year age group (27%) with more than twice as many reports in males than females. Risk factor information is available for 57% of cases and the commonest risk factor is injecting drug use (80%) followed by receipt of blood products and transfusions (10.8%).

2.1.4 During 1996, national surveillance of blood borne infections in UK donors indicated that 0.06% of new donors were anti-HCV positive. This compares to 0.28% in France, 0.16% in Germany and 0.04% in Denmark. It is important to realise that blood donors are a self-selected group of patients expected to have lower rates of infection than the general population. The transmission of HCV by blood and blood products in the UK has been virtually eliminated through exclusion of infected donors and by virus inactivation procedures. The risk of an infectious blood donation entering the blood supply is less than 1 in 200,000 in England.

Parenteral Transmission

2.1.5 The main route of HCV transmission is parenteral, and the majority of patients will give a history of either intravenous drug abuse or a blood/blood product transfusion prior to anti-HCV testing. In 1989 Zuckerman reported the presence of anti-HCV antibody in 85% post-transfusion hepatitis patients, 60-80% of haemophiliacs receiving blood products, 60-70% of cases of chronic liver disease with a history of blood transfusion and 50-70% of intravenous drug abusers [13]. Application of second generation diagnostic tests and PCR suggest that some of these figures are underestimates [14]. Long-term follow up indicates that a large proportion of those patients infected by blood or blood product transfusion will develop chronic viral carriage[15] [16]

2.1.6 Intravenous drug abuse is a major risk factor for HCV infection with between 50-100% of IVDUs being anti-HCV positive. Other parenteral routes of transmission include haemodialysis[17] [18], organ transplantation[19], tattooing and in certain countries traditional practices using non-sterilised knives and indeed the use of non-sterilised needles in large scale immunisation programmes may have contributed to the spread of HCV in these communities. Transmission has also been documented following needle stick injuries (risk estimated 1.8% CDC 1997), but the frequency of seroconversion following needlestick exposure seems to be low[20], and the prevalence of HCV infection

in health-workers is no greater than in the general population[21].

Non-Parenteral Transmission

Sexual Transmission

2.1.7 Epidemiological studies show low rates of HCV infection in high promiscuity groups such as prostitutes, homosexuals and patients with sexually transmitted diseases[22-24] and suggest a limited role for sexual transmission. A more recent study showed a seropositivity rate of 11.7% in HIV positive homosexuals who did not have a history of transfusion or IVDU suggesting that sexual transmission occurs and may be facilitated by coinfection with HIV[25]. Although Alter suggested in 1989 that heterosexual contact was responsible for a proportion of acute NANB cases, more recent studies have failed to support these findings[26] [27]. Indeed Hsu[28] was unable to detect HCV by PCR in semen, urine, stool or vaginal secretions. The overall rate of anti-HCV positivity appears low in sexual partners of HCV infected haemophiliacs[29] unless there is coexistent HIV infection. In one study intraspousal infection was confirmed by sequence analysis of the E1 gene[30] although the risk of transmission in long term monogamous relationships is less that 5%[31] [32]. However multiple sexual partners, sexually transmitted disease clinic attendance and prostitution are associated with an increased risk of HCV infection[33].

Vertical Transmission

2.1.8 The risk of vertical transmission seems to be low (<6% of children becoming HCV positive) unless the mother is HIV positive or has a particularly high level viraemia[34-37]. Breast feeding has not so far been implicated in HCV transmission and the virus has not been found in breast milk[38] [39].

Alternative Routes of Transmission

2.1.9 In families inapparent parenteral exposure may occur, perhaps by sharing razors or toothbrushes. HCV has been found in saliva[39-41] and in one study NANB was thought to have been transmitted from chimpanzees by saliva[42]. Studies of non-sexual household contacts of HCV seropositive patients have reported seroprevalence rates varying from 0.5% to 13%[43] [44].

2.2 Natural History of HCV infection

2.2.1 Sub clinical HCV infection is the rule with only 10% patients reporting an acute illness associated with jaundice. HCV infection rarely causes fulminant hepatitis[45] [46] but severe acute HCV infections have been reported in liver transplant recipients[19], patients with underlying chronic liver disease and in patients coinfected with HBV[47]. Although the acute illness is usually mild, a high proportion of patients progress to chronic liver disease[8]. In a study of 135 patients with post-transfusion hepatitis (PTH), 77% developed chronic disease and of the 65 patients with sequential liver biopsies, 32% had developed cirrhosis after a mean follow up of 7.5 years[16]. Only 1% of these patients had a histological remission with the remaining patients having chronic active (CAH) or chronic persistent hepatitis (CPH). However in the same year Seeff published a long term follow up study of patients with post-transfusion NANB hepatitis[48]. 568 patients with PTH and two control groups of 526 and 458 patients who had received transfusions without developing hepatitis were studied. After an average follow-up of 18 years the mortality related to liver disease was 3.3% in PTH cases compared to 1.5% in the control groups and the majority of deaths occurred in patients with associated alcoholism. It appears therefore that most patients who develop progressive disease do so slowly.

2.2.2 In 1995 Tong published a study of 131 post transfusion hepatitis cases referred to a centre between 1980 and 1994[49]. 101 patients underwent liver biopsy a mean of 22 years post transfusion. Twenty-seven (20.6%) had chronic hepatitis, 30 (22.9%) had chronic active hepatitis, 67 (51.1%) had cirrhosis, and 7 (5.3%) had hepatocellular carcinoma after mean time intervals from transfusion of 14, 18, 20 and 28 years respectively. During the follow up period 20 (15.3%) patients died, 19 (95%) from complications of cirrhosis or the development of hepatocellular carcinoma. Thus persistent post-transfusion HCV infection does lead to progressive liver disease and in some patients death from related liver failure or the development of hepatocellular

carcinoma although long follow up studies are required to assess the contribution of HCV to morbidity and mortality. However most studies have been conducted at referral centres, reflecting the severe end of the disease spectrum, so that the true numbers of patients with non-progressive or mildy progressive liver disease remains unknown.

2.2.3 Viral factors associated with more rapidly progressive disease include high level viraemia[50], genotype 1 (especially 1b)[51] and the degree of viral genetic diversity (quasispecies)[52] [53]. Route of transmission may be important as patients infected via blood transfusion tend to have more histologically active liver disease[27]. Other host factors such as immune deficiency[54], excess alcohol[55] [56] and coinfection with HBV[47] and HIV[57] may also influence the rate of disease progression.

2.2.4 There is a variable rate of fibrosis progression with a median time from infection to cirrhosis of roughly 30 years (range 13-42 years)[58]. Independent factors associated with an increased rate of fibrosis progression include age at infection greater than 40 years, daily consumption of 50g or more of alcohol, and male sex. There was no association between fibrosis progression and genotype.

2.2.5 In HCV associated compensated cirrhotics the 5 year survival is over 90% and 10 year survival 80%[59]. A 5 year follow up showed the risk of developing HCC was 7% (1.4% per year) and 18% decompensated. After decompensation, the prognosis is poor with 50% survival at 5 years.

2.3 Clinical spectrum of disease

2.3.1 Infection with the hepatitis C virus results in a variety of hepatic and extrahepatic diseases. In a minority of patients, infection results in an acute hepatitis with symptoms resembling other forms of acute hepatitis[4]. The mean incubation period is 7 weeks and symptoms, if present, last for 2-12 weeks. There are, however, few reliable studies on the natural history of acute HCV and although the minority of patients clear the virus, the precise numbers are not known.

2.3.2 Patients with chronic HCV often have no symptoms but may complain of non-specific complaints such as fatigue, muscle aches, anorexia, right upper quadrant pain and nausea. Symptoms and signs of chronic liver disease occur later in the disease. However some patients with chronic HCV cirrhosis remain asymptomatic. Thus the presence of symptoms is a poor marker of the severity of liver disease.

2.4 Extrahepatic Manifestations

2.4.1 HCV infections have been associated with a number of immunologic disorders including autoimmune hepatitis (AIH), Sjogren's syndrome, Lichen planus, thyroiditis, membranous glomerulonephritis, and polyarteritis nodosa[60]. HCV is associated with essential mixed cryoglobulinemia (EMC)[61-63].

2.4.2 Recognition of HCV involvement in disorders such as cryoglobulinaemia and idiopathic thrombocytopenic purpura[64] will allow consideration of interferon therapy for these non-hepatic as well as hepatic diseases.

2.5 HCV and alcohol

2.5.1 There are high rates of HCV antibody positivity amongst alcoholic patients[65] [66]. Most of the antibody positive patients are also HCV RNA positive and some studies suggest higher levels of HCV RNA in this group of patients[67], although this remains to be confirmed. The presence of anti-HCV antibodies is associated with more severe liver disease in alcoholic patients.

2.5.2 The importance of alcohol in chronic HCV infection was shown in Poynard's recent study showing a daily consumption of more than 50g of alcohol is associated with an increased rate of fibrosis progression[58].

2.6 HCV and hepatocellular carcinoma

2.6.1 HCV infection is associated with a large proportion of hepatocellular carcinomas (HCC's). In southern Europe and Japan 50-75% of HCC are associated with HCV[65] [68-70]. HCV may cause HCC as a consequence of cirrhosis or as a result of chronic necroinflammation rather than having any direct carcinogenic effects. Unlike HBV, HCV does not integrate into the host's DNA. The majority, if not all, of patients with HCV associated HCC have established cirrhosis. Both HBV coinfection and excess alcohol seem to have an additional effect on the development of HCC[71] [72].

2.6.2 The natural history of disease progression is slow in HCV related liver disease with estimates of 20-30 years duration of infection prior to the development of HCC[49]. In patients with established cirrhosis the rates of development of HCC range between 1-7% per year[59] [73]. The role of antiviral therapy in preventing the development of HCC in HCV infected cirrhotics is controversial[73].

3.0 Diagnosis

3.1 Diagnostic serological assays

3.1.1 The discovery of HCV in 1989[74] led to the development of an antibody diagnostic assay based on viral recombinant peptides. The first generation tests incorporated a fused antigen of human superoxide dismutase (SOD) and HCV polypeptide (C100-3) used in an enzyme linked immunosorbent assay (ELISA)[75]. The first generation assay lacked sensitivity and specificity prompting the development of second generation assays incorporating antigens from the nucleocapsid (C22) and NS3 (C33) genomic regions. Third generation assays (ELISA-3) have since been introduced incorporating antigens from the putative nucleocapsid, NS3, NS4, and NS5 regions. ELISA-3 tests have a sensitivity of 97% and have shortened the mean time to seroconversion by 2-3 weeks[76]. ELISA-3 tests are now the most widely used screening test for HCV[77] [78] but despite the improved specificity confirmation of positive results is still required as a significant proportion of positive tests will represent false positive results. The false positive rate is especially important in low prevalence settings where the number of false positives may exceed the number of true positives.

3.1.2 A positive ELISA test in a patient with chronic liver disease is probably enough to diagnose HCV infection and a confirmatory antibody test may not be needed. Confirmatory PCR testing of the serum for HCV RNA is suggested for this group of patients.

- Patients with suspected HCV infection should be tested for anti-HCV by an up-to-date (currently third generation) ELISA test (B).

3.2 Confirmatory assays

3.2.1 By immobilising HCV antigens on to nitrocellulose strips recombinant immunoblot assays were developed (e.g Chiron RIBA,Chiron Diagnostics) for confirmation of positive ELISA results. A first recombinant immunoblot assay (RIBA-100) was developed with separately immobilised C100-3, 5-1-1 and SOD antigens.

3.2.2 Second generation RIBA tests were developed with antigens from nucleocapsid (C22) and NS3 (C33) in addition to C100-3 and 5-1-1. Both chimpanzee[79] [80] and human studies[81-84] have suggested that second generation tests allow earlier detection of HCV infection in acute cases and are more frequently positive in chronic cases. A positive second generation RIBA result is associated with HCV viraemia by PCR in 88-98% of cases[85-87].

3.2.3 A positive RIBA test is associated with reactivity with two or more of the antigens, and in the majority (63%) of cases[88] reactivity to all four antigens is detected. An indeterminate result

shows reactivity to any one antigen. Several studies have shown that reactivity with c100-3 or 5-1-1 alone is rarely associated with PCR positivity and can be regarded as falsely positive[86] [88-90]. The majority of patients with lone antibody to c33 and about half of those with antibody to c22 will be PCR positive and therefore represent true positive results[86] [88] [89] [91] [92].

3.2.4 Third generation RIBA tests have been developed incorporating synthetic C22 and C100-3, recombinant C33 and a recombinant NS5 antigen expressed in yeast to replace 5-1-1. This later version has been shown to be positive in most RIBA-2 indeterminate cases[90] [93] and to correlate better with HCV viraemia[94]. However despite the improved sensitivity of this test, indeterminate results have been observed and HCV RNA is detected in 58% of these cases[95]. Thus patients with indeterminate RIBA-3 results must be evaluated for evidence of viral replication and liver disease.

3.2.5 Following a positive antibody test, patients should be referred to the nearest specialist service for further clinical assessment. Specialist clinicians will be responsible for the care of these patients and will ensure some uniformity of approach, whilst facilitating data collection, audit and research.

3.3 The Polymerase Chain Reaction

3.3.1 Initial PCR for HCV detection used primers derived from heterogeneous non-structural regions of the virus. The development of primers from the highly conserved 5' non-coding region greatly enhanced the detection of HCV RNA by PCR[96]. The sensitivity of PCR detection was further enhanced by the development of PCR primers producing shorter PCR products[96]. The sensitivities of most PCR assays is in the range of 500-1,000 equivalents per ml.

3.3.2 Direct detection of the virus using polymerase chain reaction (PCR) is needed in patients recently infected with the virus and in immunosuppressed individuals who may be antibody negative. In addition PCR is useful for determining the status of patients with indeterminate antibody profiles and for monitoring antiviral therapies. The sensitivities and specificities of the commercially available PCR tests are very high. Intermittent viraemia is unusual in patients untreated with interferon so enhancing the significance of a negative PCR result[97].

- All patients with positive antibody tests and those patients thought to be at risk of HCV infection despite negative or indeterminate serological tests should undergo PCR testing of the serum. A positive result confirms current viraemia whereas a negative test suggests non-viraemic infection, transient absence of viraemia or recovered infection, a level of viraemia below the detection limit of the assay or may reflect a non-specific ELISA result (B).

- Patients with positive ELISA but negative PCR should therefore be tested with recombinant immunoblot assay to confirm antibody status (C).

- A qualitative PCR test is recommended in immunodeficient patients with suspected HCV infection (B).

3.4 Liver tests

3.4.1 The use of routine liver tests to screen for chronic hepatitis C virus infection is of limited value as about 50% of HCV infected (anti-HCV and PCR positive) patients will have normal transaminase values. Despite normal liver tests these viraemic patients should not be considered "healthy carriers" as the majority will have histological evidence of necroinflammatory liver disease with or without cirrhosis[98]. Other studies have shown that transaminase levels can be helpful in predicting severity of liver disease, with higher levels associated with more advanced histology, but that they are of limited value in an individual patient[99].The value of monitoring transaminases is limited with levels fluctuating from normal to abnormal over time.

- The results of routine liver tests correlate poorly with both necro-inflammatory and fibrosis scores found on liver biopsy (B).

3.5 Liver Histology

3.5.1 Liver biopsy is usually performed before initiation of antiviral treatment and remains the most accurate measure of the extent of liver disease. Liver biopsy is usually done in patients with evidence of chronic HCV infection with abnormal transaminases who are being considered for antiviral therapy. In addition histological information is useful when other diagnoses such as alcohol induced liver disease are being considered.

3.5.2 The role of liver biopsy in patients with normal transaminases is less clear. Several studies have shown that patients with normal transaminases often have evidence of significant liver disease on liver biopsy. In one study 11% of 54 patients with CAH or active cirrhosis had normal ALT[100], and in another more than 50% of patients with CAH, CPH or cirrhosis had normal ALT levels[101]. Liver biopsy may be considered in HCV positive patients with normal LFT's and positive for HCV RNA who are being considered for treatment.

3.5.3 In a further study the use of clinical parameters to predict cirrhosis was found to be inaccurate with a correct diagnosis in less than one third of cases[102]. In the absence of a less invasive measure of fibrotic liver disease, liver histology remains the gold standard for the assessment of the severity of liver disease.

3.5.4 The biopsy appearance at presentation does not predict the rate of disease progression in an individual non-cirrhotic patient but biopsies taken every 2-3 years may be useful in predicting outcome if there is progressive accumulation of fibrous tissue.

3.5.5 Some patients will test positive for antibody to HCV, have abnormal LFT's but will be PCR negative: these patients should be screened for other liver diseases including autoimmune hepatitis and haemochromatosis. Anti-HCV positive patients found to be PCR negative with normal ALT's should probably be followed up annually until the natural history (virological and biochemical relapse rate) is better known: liver biopsy may be recommended if there is a return of viraemia or a flare up of liver enzymes.

· Liver biopsy is valuable for assessing status of liver inflammation, potential progression of fibrosis and the presence or absence of cirrhosis. To clarify these, and to assess suitability for treatment, liver biopsy is recommended for patients found to be viraemic, whether or not liver function tests are abnormal. Standard histological scoring systems by a suitably experienced pathologist, should be used to encourage uniformity of histological reports. The risks and benefits of liver biopsies must be fully discussed with the patient (B).

3.5.7 Liver biopsy is probably not indicated after a course of treatment in the majority of patients. A repeat liver biopsy at a remote time interval will provide information on disease progression in both responders and non-responders but the precise timing is not clear and so probably is not recommended outside the setting of a clinical trial.

3.6 Assessment of viraemia

3.6.1 Measuring the level of HCV RNA in blood samples has been widely reported with some studies showing varying levels with changes in LFT's[103] and others suggesting stable levels in individual patients prior to treatment[97]. However the role of HCV quantitation in determining disease course remains unclear but the results of recent trials suggest that levels of viraemia are important in tailoring IFN/Ribavirin combination therapy. The level of HCV viraemia can be measured by quantitative PCR[103-105] or by signal amplification techniques such as branched DNA assay.

3.7 Genotyping

3.7.1 Analysis of the conserved 5'NCR allowed the distinction of 3 major groups, types 1, 2 and 3. Analysis of samples from around the world led to the discovery of other

genotypes. Type 4 HCV was found predominantly in the Middle East and Egypt[106], type 5 sequences were found only in South Africa[107] [108]. More recently type 6 has been described from Hong Kong[109].

3.7.2 Phylogenetic analysis of the NS5 region has allowed the classification of HCV into 6 major genetic types and a number of subtypes. So far there has been no overlap in sequence variability between the different classes with nucleotide homologies of 88-100% between isolates, 74-86% between subtypes and 56-72% between types.

3.7.3 Typing can be performed in several ways, either serologically with specific peptide ELISA's (serotyping)[110], or by analysis of PCR products. The latter can be carried out by direct sequencing[111] [112], with type specific primers[113], on the basis of restriction fragment length polymorphisms (RFLP's)[114] or with sequence specific DNA probes (genotyping)[115]. Genotype helps predict the rate of disease progression[116] [117] and response to antiviral treatment[118] [119].

- The measurement of HCV RNA concentrations in serum and the determination of HCV genotype are recommended and should be used to determine the duration of treatment (see later) (A).

4.0 Treatment

4.1 Counselling

4.1.1 The diagnosis of HCV causes considerable anxiety to patients and it is therefore essential that all patients receive adequate counselling from a health carer with knowledge and experience in this field. The natural history, treatment options and likelihood of success should be discussed. Patients should be reassured that HCV infections are not usually associated with other infections such as HBV or HIV. Although the precise role of sexual transmission remains to be established[26] [32] [120] [121], because up to 5% of spouses of infected patients are infected[30] [31] [122], couples in new relationships should be advised to use barrier contraception. In established relationships the small risk of transmission should be explained and the couple should be reassured and left to decide whether to change their sexual practices. The risk of vertical transmission seems to be low (<6% of children becoming HCV positive) unless the mother is HIV positive or has a particularly high level viraemia[34-36]. Mothers should be advised that breast feeding is probably safe and that so far HCV RNA has not been demonstrated in breast milk[38] [39].

Counselling regarding transmission

- Patients should be counselled on the implications of HCV positivity and advised on the risks of infectivity:
    - the natural history is slowly progressive (median time to cirrhosis = 28-32 years) (A).
    - HCV positive patients should not donate blood, organs, tissues or semen (C).
    - the risk of sexual transmission is small - maximum of 5%, but possibly much less (B). There is insufficient evidence to firmly recommend barrier contraception (C).
    - transmission from mother to child is rare - maximum of 6%, but transmission rates are higher in HIV positive mothers (B).
    - breast feeding is not contraindicated (C).
    - ousehold contacts should avoid third party contact with blood by not sharing toothbrushes and razors, and by covering open wounds (C).
    - standard precautions for the prevention of transmission to medical personnel and patients is mandatory in health care settings (C).
    - needle exchange programs in drug addicts may help reduce parenterally transmitted

infection (C).

4.1.2 Patients must also be screened for their suitability to receive Interferon and Ribavirin therapy. The decision to treat must be taken jointly by physician and patient, based on careful consideration of a number of different factors.

4.1.3 Patients should probably not be offered Interferon (IFN) if there is a history of depressive illness, psychosis, untreated autoimmune thyroid disease, neutropenia and/or thrombocytopaenia, organ transplantation other than liver, symptomatic heart disease, decompensated cirrhosis, uncontrolled seizures or evidence of ongoing alcohol or intravenous drug abuse. Patients should have access to reliable refrigeration to store IFN and be able and willing to make regular clinic visits. Adequate warning should be given of the usual initial effects of IFN (fever and malaise) and in particular absence from work may be necessary during the early stages of treatment. Administration prior to sleep with a pre-dose of 0.5-1g of paracetomol in the initial weeks of treatment may reduce "flu-like" symptoms associated with initial IFN therapy. Severe side effects from either IFN or Ribavirin are infrequent, but they may be reversible and dose modulation may successfully reduce the occurrence of side-effects whilst maintaining therapy. Women should be advised not to conceive during a course of IFN.

4.1.4 Ribavirin is contraindicated if there is evidence of end-stage renal failure, anaemia, haemoglobinopathy, severe heart disease, uncontroled hypertension, pregnancy (a pregnancy test prior to treatment is advisable) or no reliable method of contraception. Both men and women should be advised to avoid conception during and for 6 months after IFN/Ribavirin combination treatment.

4.1.5 These guidelines apply to adults over 18 years of age, the upper age limit where treatment should be given is unclear but perhaps 65 or 70 years would be reasonable.

4.1.6 The management of patients needs to take into account the differing patient groups according to their transmission routes. These groups include current and ex-injecting drug users, blood or blood product recipients (some identified by HCV lookback) and those with unknown or in-apparent transmission (e.g sexual, vertical, household or occupational). These patient groups may well need different approaches to the way they are managed.

4.1.7 For many current IVDUs there are multiple contra-indications to therapy, in addition to concern that continued or recommencing intravenous drug use will result in re-infection with HCV. Some patients may respond to a multidisciplinary approach and anti-viral treatment may be considered within the context of detoxification and rehabilitation programmes. Many patients with a history of injecting drugs fail to re-attend for follow-up after the initial diagnosis of HCV[123]. Although current IVDUs should not be treated, some patients on oral methadone and particularly those individuals who are committed to rehabilitation programmes may be considered for treatment.

Current IVDUs should not be treated although in selected cases ex-IVDUs taking regular oral methadone may be considered for treatment (C).

4.1.8 The next large group of patients are those infected with HCV as a result of blood or blood product transfusion. The HCV look-back study has attempted to trace all recipients of HCV infected blood since the introduction of HCV antibody screening in September 1991. It has been estimated that up to 60% of these patients have died due to the original presenting diagnosis, so that the numbers of infected patients presenting for treatment are smaller than originally estimated. One of the most significant issues with those identified by "HCV look-back" is the impact of a new and otherwise unsuspected diagnosis with the risks of significant liver disease. The effects on partners, family and offspring must be considered. These include issues such as prognosis, infection risk, financial and insurance prospects and possible medico-legal action. Support and follow-up for close contacts of the recipient case is important as they need access to information, counselling and follow-up depending on results of antibody testing.

4.1.9 The group of patients infected by blood products is similar to that infected by blood but may already be affected by the dissemination of HBV or HIV. There is debate about the health impact of HCV on patients with genetic clotting disorders as well as the need for intervention, including

liver biopsy, monitoring or non-intervention[124]. The risks and costs of performing liver biopsy are greater than in other groups of patients and in many of these patients the consequences of the clotting disorder or of co-infection with HBV or HIV are more of a health concern than chronic HCV. The management of patients co-infected with HIV is also controversial, particularly in view of recent developments in antiviral therapy.

4.1.10 An estimated 2-5% of chronic HCV infected patients have no behavioural risks, but all of the above routes may be the source of possible transmission along with others such as tattooing and poor sterilisation of re-used medical instruments.

4.1.11 Significant numbers (up to 40%) of patients do not accept treatment or complete the full course of treatment or follow-up[123], particularly in those patients with a history of injecting drugs. Even in those with moderately severe disease, a significant number (42%) did not want to undergo treatment.

4.1.12 The role of patient support groups at local and national level is to be encouraged and perhaps facilitated in the primary care setting. The British Liver Trust organise a national support group network and help in starting up new groups (telephone: 01473-276326).

4.2 Treatment - general measures

- Patients should be advised that excess alcohol consumption (50 g/day) appears to hasten the progression of disease (B).

- Consideration should be given to entering patients with established cirrhosis into surveillance programmes for hepatocellular cancer, if their general state of health is sufficiently good that emerging cancers could be appropriately treated (C).

- Patients must be screened for their suitability to receive Interferon and Ribavirin, with criteria which includes proven viraemia and abnormal liver histology (C).

4.3 Antiviral Therapy

4.3.1 The treatment of HCV has evolved from the use of single agent IFN to the use of combination treatment using IFN and Ribavirin.

- Interferon (IFN) and Ribavirin are currently the only licensed treatments for HCV in the United Kingdom.

- IFN/Ribavirin combination is the treatment of choice for IFN naive patients (A).

- IFN/Ribavirin combination is also recommended for those patients relapsing after IFN monotherapy (A).

- IFN monotherapy should be considered for those patients in whom ribavirin is contraindicated (C).

4.4 IFN monotherapy

4.4.1 Numerous studies have now been published to evaluate differing interferons, dosing regimens and response definitions. The disparate study designs and data analysis make interpretation of the results and comparison with other studies difficult. Few trials have included more than 100 patients per treatment group[125].

4.4.2 The goal of treatment is the achievement of sustained (24-48 weeks post treatment cessation) transaminase and virological response (PCR negative) with histological improvement. Most of the treatment trials have used similar doses of between 1-3 million units of interferon three times a week for periods of three to six months. A dose of 3 million units is more efficacious than 1 million units[126]. In addition only those patients receiving 3 MU had significant improvements in liver histology. Alberti et al have shown that 6MU 3x/week leads to a higher proportion of patients with normal ALT at the end of treatment compared to those treated with 3MU 3x/week[127]. Another study using 10 million units three times a week suggested that sustained response rates could be as

high as 50% although there is a greater risk of treatment failures due to side effects[128].

4.4.3 Longer treatment regimens of 12 or 18 months also resulted in greater numbers of sustained responders. In one study with a 3 year follow-up period, treatment for 48 weeks led to a sustained biochemical response in 57.1% of patients compared to 15.4% in patients treated with the same dose for 24 weeks[129]. One large trial studied 329 patients treated initially with 3 MU 3x/week for 6 months and then randomised to a further 1 year of 3 MU or 1 MU 3x/week or no further treatment[130]. 303 patients were randomised and the study end-points were normalisation of ALT at the end of treatment, during a follow-up period of 19-42 months and improvement in histology at the end of treatment. The patients treated with 3 MU for 18 months were more likely to have normal ALT at the end of treatment (p=0.008), during follow-up (p=0.02) and to have improved histologic-activity scores at the end of treatment (p=0.02).

4.4.4 The majority of patients (90%) with sustained response seem to maintain normal ALT with negative HCV-RNA in prolonged follow-up (1-6 years)[131]. The histological appearances also improve and in some patients the liver becomes normal.

4.4.5 Poynard at al published a meta-analysis of more than 100 randomised interferon trials[125] in 1996. The study analysed placebo controlled trials as well as trials using different IFN regimens. Trials were included if they were clearly randomised, using IFN alone and were using at least one of the following clinical end-points: normalisation of ALT during and at the end of treatment (complete ALT response), sustained ALT normalisation (sustained ALT response 6-18 months post treatment cessation), and improvement in histological lesions when biopsy after treatment was compared with biopsy before treatment. Trials were only included if the dose of IFN was at least 3MU three times per week with a duration longer than 6 months. All patients were IFN naive.

IFN vs Placebo

4.4.6 Using the standard regimen, 3MU three times per week for 6 months, the sustained response rates were 22% when compared to a natural course of 1%. The response rates were improved when treatment was continued for 12 months with sustained response in 38% compared to 2% in controls. In a smaller number of studies using 6 month treatment, histological improvement was demonstrated in 67% versus 14% in the control group ($p<0.001$). The discrepancy between ALT and histological responses may reflect a natural tendency towards a decrease in histological activity but also may be due to the marked variability in histological endpoints.

Dose Effect

4.4.7 In the trials studied for the effects of differing doses of IFN, there was no significant difference between 3MU or 6MU given for 6 months although there was a tendency for greater response rates in the group taking the higher dose. However there was a significant improvement in response rates at 12 months for the higher dose in terms of complete response ($p=0.005$) and sustained response ($p<0.001$). The mean sustained response rate in the 6MU group was 46% versus 28% in the 3MU group. However dose reduction due to side-effects was more common in patients treated with doses of more than or equal to 5MU (22%) compared to those on 3MU (9%) ($p=0.01$).

- We recommend IFN monotherapy should be initiated at a dose of 3MU three times per week by injection (B).

Duration Effect

4.4.8 In the meta-analysis longer duration of treatment did not significantly effect the numbers of patients with complete ALT response but did alter the rate of sustained response. At standard doses of 3MU the mean sustained response rate in the 12-18 month group was 35% versus 14% in the 6 month group ($p<0.001$). The mean sustained response for the higher dosing regime (6MU) was 49% for 12-18 month treatment compared to 29% in the 6 month group ($p<0.001$).

- IFN monotherapy should be continued for 12 months unless there is evidence of failure to respond (see below) (B).

Type of Interferon

4.4.9 Four forms of ?-IFN have been evaluated in adequate numbers of HCV infected patients: alfa-2b, alfa-2a, alfa-n1 and consensus interferon (CIFN). Both alpha-2b and -2a are produced by recombinant DNA techniques using a strain of E.coli genetically engineered to possess plasmid DNA containing an IFN gene from a human leucocyte. Alpha-2b differs from -2a by a single amino acid. Interferon alpha-n1 is a mixture of 9 IFN subtypes produced from a human B lymphoblastoid cell line while consensus IFN was produced by scanning subtypes of IFN and assigning the most frequently observed amino acid at each position to form a consensus molecule.

4.4.10 There are relatively few studies that directly compare the different types of alpha IFN. In one study comparing alfa-2a to alfa-2b, 32 patients were given 6MU alfa-2a and 68 patients given 5MU alfa-2b each three times a week for 12 months. The prolonged response rates were similar (25% alpha-2a vs 19% alpha-2b) and side-effects were similar suggesting no major differences between the drugs. Comparisons between alfa-2a and lymphoblastoid IFN (alfa-n1) suggest no significant differences in terms of efficacy but there may be more frequent side-effects in the patients receiving lymphoblastoid IFN[132].

4.4.11 In one large multinational study involving 1071 patients the efficacy and safety of lymphoblastoid IFN (alpha-n1 - Wellferon) was compared with recombinant alpha-2b given for 24 weeks in IFN naive patients[133]. At the end of treatment both biochemical (36.6%) and virological responses (IFN alpha-n1 37.9% vs IFN alpha-2b 42%) were similar. Tolerability and severity of reported side-effects were similar in the two groups. During follow-up relapse was more common in patients treated with IFN alpha-2b with sustained virological response at week 72 of 8.5% in those treated with IFN alpha-n1 compared to 4.8% in those treated with IFN alpha-2b (p=0.04). In the vast majority of patients with a sustained response at one year, liver biopsy specimens showed improvement, but there were no differences between the two types of IFN. Thus lymphoblastoid IFN seems to be at least as efficacious as recombinant IFN's and may reduce the post-treatment relapse rate.

4.4.12 Further studies have compared consensus interferon (CIFN) with recombinant IFN (IFN alfa-2b) and have shown similar efficacy profiles and side-effect profiles. However this type of IFN has not been used as so often in clinical practice and further studies are needed to determine whether it should be used in place of recombinant or lymphoblastoid IFN. The data from trials using other forms of IFN such as pegylated IFN are expected soon and initial reports suggest encouraging results.

- There is no evidence to suggest that one type of alfa-interferon is superior to another (alfa-2b, alfa-2a, alfa-n1 and consensus interferon (CIFN) (B).

4.5 Interferon/Ribavirin combination therapy

4.5.1 Ribavirin is a nucleoside analogue that is well absorbed orally and has broad antiviral activity against a variety of DNA and RNA viruses. Ribavirin is administered in doses of 1,000 to 1,200 mg/day depending on body weight (above/below 75kg).

Ribavirin Monotherapy

4.5.2 Initial pilot studies with Ribavirin revealed encouraging results with significant biochemical responses during treatment, however there was always a relapse following treatment withdrawal. There was no effect on HCV viraemia[134] [135].

4.5.3 More recently randomised, double-blind, placebo controlled trials of ribavirin therapy have been reported. Once again there were biochemical responses in most patients treated with ribavirin, but no patient became persistently PCR negative[136-138].

Combination Therapy

4.5.4 Initial pilot studies revealed encouraging results with the combination of Interferon

and Ribavirin[139], particularly in patients who had relapsed after an initial course of alpha interferon[140]. Studies in Interferon naive patients also showed beneficial effects of combination treatment over Interferon alone. Two European studies revealed improved sustained response rates of 47% and 60% in the combination groups when compared to interferon alone[141] [142].

4.5.5 The results of a randomised, double-blind, placebo-controlled trial of interferon alpha-2b with and without ribavirin for chronic hepatitis C have recently been published[143]. One hundred IFN naive patients were randomly assigned to treatment with interferon alpha-2b (3 MU three times per week) in combination with ribavirin or placebo for 24 weeks and then followed-up for a further 24 weeks. The primary endpoint was sustained virological response at 24 weeks and 1 year. 18/50 (36%) of the patients treated with combination therapy had a sustained virological response compared with 9/50 (18%) treated with interferon alone (p=0.047). At 1 year follow-up the proportion of patients with a sustained virological response was greater in the combination therapy group (42 vs 20%, p=0.03). Interestingly the beneficial effect was most pronounced in patients with high level viraemia.

4.5.6 In the latter half of 1998 two further randomised studies were published on IFN/Ribavirin combination therapy in HCV IFN naive patients (see table 1). In the French study 832 IFN naive patients were randomised into one of three treatment groups: IFN 3mu three times per week plus Ribavirin 1000-1200mg/day for 48 weeks, IFN plus Ribavirin in the same doses for 24 weeks and IFN plus placebo given for 48 weeks[144]. The primary endpoint was loss of HCV-RNA at 24 weeks after therapy. The sustained viral clearance rates were 43% for the 48 week combination therapy, 35% for the 24 week combination therapy and 19% for the 48 week IFN monotherapy. Although the difference between 48 and 24 week monotherapy did not reach significance (p=0.055) the differences between both combination regimes versus monotherapy were highly significant (p<0.001).

4.5.7 In the American Hepatitis Interventional Therapy Group Study 912 IFN naive patients were randomly assigned to combination therapy for 24 or 48 weeks or IFN monotherapy for 24 or 48 weeks[145]. The primary endpoints were virological response (definined as sustained response) and histological improvement at 24 weeks after therapy was discontinued. The virological response rates were 31% and 38% for the combination groups (24 and 48 weeks therapy) and 6% and 13% for IFN monotherapy (p<0.001 for comparisons of monotherapy to both combination regimes). Improvements in histology were seen in 57% and 61% of cases treated with combination therapy versus 44% and 41% for the monotherapy groups. Of the 165 patients who had a sustained virological response, 142 (86%) had a decrease in hepatic inflammation regardless of the treatment regimen. Inflammation was also seen in 39% who had persistent viraemia in follow-up.

4.5.8 The results of these randomised studies suggest that combination therapy leads to a sustained virological response in roughly 30-40% of IFN naive patients (a 2-3 fold better response when compared to IFN monotherapy - see tables 1-3) . Although greater numbers of patients do not complete the course of treatment due to unwanted side-effects, the improved response rates suggest that combination therapy is the treatment of choice for HCV infection. Sustained responses of 29% for 24 weeks and 38% for 48 weeks were achieved in cirrhotic patients (see table 4).

- Recent results of large randomised controlled studies have shown improved response rates for IFN/Ribavirin combination therapy in IFN naive and relapsers when compared to IFN monotherapy (A).

- Combination therapy consists of IFN at standard doses (usually 3MU three times per week) with Ribavirin 1000mg/day for patients weighing 75kg or less and 1200mg for those weighing more than 75kg (A).

4.6 Who to treat - according to biopsy

4.6.1 The decision of whether to treat is complex. As the treatment is relatively expensive and does not cure most cases, patients need to be selected as those most likely to

respond to treatment and also those in whom the impact of treatment is greatest, in terms of halting disease progression and preventing complications. Decisions about treatment should be made after liver biopsy has been performed and patients classified into mild, moderate or severe disease categories according to the histological appearances. Histological appearances are classified as mild if the fibrosis score (Stage) is less than or equal to 2/6, and if the necroinflammatory score (Grade) is less than or equal to 3/18. If the fibrosis score is 3-5/6 and/or the necroinflammatory score is greater than 3/18, the appearances are described as moderate. If the fibrosis score is 6/6 the biopsy is cirrhotic irrespective of necroinflammatory score.

4.6.2 All liver biopsies should be examined by a histopathologist with experience in liver pathology and who can apply the recently reformed grading and staging scores[146]. Some pathologists prefer to base the assessment of severity of hepatitis on individual components of the grading system. In this case mild hepatitis can be defined as having scores for interface hepatitis and for lobular hepatitis of 0 or 1 out of 4. Confluent necrosis should be absent (score 0). Any grade of portal inflammation is acceptable.

4.6.3 In patients with mild, slowly progressive disease it may be best to withhold treatment until more efficacious treatments are available. Others would regard this as the best time to treat, perhaps resulting in higher numbers of responders, and others would argue that the virus rather than the disease process needs to be treated and so all infected patients need to be considered for treatment.

Mild disease

4.6.4 Patients with mild disease at presentation represent up to 25% of patients attending for consideration of treatment. These patients are potentially infectious, and despite minimal disease on liver biopsy, may suffer long-term consequences of chronic liver disease. Alternatively treating these generally clinically well patients with expensive drugs with potentially serious side-effects may well be inappropriate unless there is clear evidence of disease progression over time.

4.6.5 Many of these patients have normal serum transaminases, although liver biopsy examination reveals some degree of histological abnormality. A recent review of 11 studies revealed that 29% of such patients had mild or non-specific changes, most (54%) had mild changes, but 19% had chronic hepatitis with moderate degrees of necroinflammatory activity[147]. These mild disease patients probably will have progressive disease, but progression is slow and the patient's life expectancy may therefore not be affected by HCV infection.

4.6.6 Several small studies have tended to show similar response rates with IFN monotherapy to trials of patients with abnormal ALT's and more severe histological changes[148] but other studies suggest that treatment in this group of patients is ineffective[147].

4.6.7 At present it is probably appropriate not to treat patients with mild disease on liver biopsy but these patients should be reviewed every 6 months with repeat liver biopsy every 2-3 years or if there is a significant change in the liver function tests (i.e 2-3 times normal levels). If the biopsy reveals worsening necroinflammatory disease and/or fibrosis then treatment should then be considered. In some cases of mild hepatitis treatment may be instigated at this early stage because of concern about infectivity. The results of trials assessing the response to IFN/Ribavirin combination are awaited.

Moderate disease

4.6.8 This group of patients are the most important group as successful treatment is likely to have the greatest impact by, hopefully, preventing progression to cirrhosis and its complications. Therefore all patients with moderate or severe inflammatory activity with or without fibrosis and any patient with fibrosis not amounting to cirrhosis on liver biopsy should be offered treatment.

Cirrhotics

4.6.9 HCV cirrhotics are an important group of patients and studies have shown that liver complications are responsible for 70% of the mortality of HCV cirrhotics[59].

Compensated Cirrhosis

4.6.10 Initial studies suggested a poorer response to IFN monotherapy in cirrhotic compared to non-cirrhotic patients[149]. A recent review of 26 published trials that separated cirrhotic patients from non-cirrhotics revealed a reduced rate of ALT normalisation during therapy (27% compared to 53%)[150]. In a smaller group of patients the rate of viral clearance was also reduced (5-10% compared to 20-35%). The poor response is more often due to failure to respond rather than to relapse following an initial response. Sustained response rates of 29% (24 weeks) and 36% (48 weeks) have been achieved with IFN/Ribavirin combination treatment suggesting that treatment may well be justified in this subgroup of patients with notoriously poor response to IFN monotherapy[145].

4.6.11 Other studies have assessed the effects of IFN on clinical events in cirrhotics. In one study only 16% of treated patients were rendered PCR negative on treatment, in the follow-up period of up to 7 years HCC was detected in 4% treated compared to 38% control patients (p=0.002)[73]. In two other studies the tendency to develop HCC was reduced in patients treated with IFN, with a particularly strong effect in those few patients with sustained biochemical and virological responses[151] [152]. However these results need to be confirmed in larger studies using IFN/Ribavirin combination with longer follow-up periods.

Decompensated Cirrhosis

4.6.12 The probability of survival after decompensation is about 50% at 5 years[59]. There is little data on the use of antiviral therapy in decompensated HCV cirrhotics.

- In viraemic patients, the decision to offer treatment should be influenced by the histological findings (B):
    - treatment can be reasonably withheld in patients with mild disease (see text) but they should be followed to see if there is evidence of progressive liver disease by the use of repeated biopsy after an interval (C).
    - treatment should be offered to those patients shown to have moderate disease (C).
    - cirrhotic patients respond less well to IFN monotherapy but sustained responses have improved with IFN/Ribavirin combination treatment. There is no conclusive evidence that treatment in this group of patients delays progression of liver disease or the development of hepatocellular carcinoma (B).

4.7 Predictors of response

4.7.1 Several factors have been implicated but their accuracy in predicting a response in individual patients has been poor. However some physicians exclude patients from treatment if they have one or more of the pre-treatment markers associated with a reduced likelihood of response in an attempt to improve response rates and improve efficiency of antiviral treatment.

Pre-treatment factors

4.7.2 Both host and viral factors have been identified by either univariate or multivariate analyses. One initial study suggested a more favourable outcome in young females and in patients with lower pre treatment ALT levels[126]. Other studies have failed to link female sex to better response but have confirmed that younger patients tend to respond more favourably[127] and that pre treatment ALT and gamma-GT levels tend to be lower in responders[153]. The better response in younger patients may reflect a shorter duration of infection in association with less severe histological lesions. Indeed several studies have shown that absence of cirrhosis and low fibrotic histological scores are associated with better treatment outcomes[119] [127]. One study reported the biochemical response rates in patients treated with IFN for 12 months according to the presence of cirrhosis or not. Within a 6 month follow-up period 5.3% of cirrhotics compared to 40.5% of non-cirrhotics showed sustained normal ALT levels[149]. Other studies have shown that the hepatic iron content of non-responders (1156+/- 283ug/g dry weight) tends to be higher compared to responders (638+/-118ug/g dry weight; $p<0.05$)[154].

4.7.3 Viral factors thought important in determining treatment response include viral genotype, level of viraemia and the level of viral heterogeneity. Improved responses are found in those

patients infected with HCV 2[118] [155] or HCV 2 and 3 compared to patients infected with genotype 1[117]. In a review of 15 interferon trials, sustained response was seen in 18.1% of HCV 1 infected patients compared to 54.9% of patients infected with other genotypes[156]. However the positive predictive value and accuracy of genotype in predicting sustained response was shown to be fairly poor (55% for predictive value, 72% for accuracy).

4.7.4 The Benelux study reported on 350 patients randomly assigned to standard IFN monotherapy (3MU 3x/week for 24 weeks) or titrated treatment (6MU 3x/week for 8 weeks followed by dose reduction based on ALT levels). 319 patients were evaluable for at least 6 months follow-up and overall the sustained response rate was no better than 14%. The titrated regime was no better than standard therapy but in multivariate analysis by logistic regression, infection with HCV 2 or 3 were independent predictors of sustained biochemical response[157].

4.7.5 Pre-treatment levels of viraemia have been studied in relation to response to IFN monotherapy. One study using a competitive PCR quantitation method revealed that sustained responders had significantly lower HCV RNA levels compared to non-responders[158]. Other researchers have used the branched DNA assay (Chiron Corporation) to measure HCV viraemia. Lau et al found that patients with sustained response to IFN had mean viraemia levels of 0.35 x 106 genomes /ml, partial responders with relapse had mean viraemia levels of 1.6 x 106 genomes/ml and non-responders had a mean viraemia level of 3.1 x 106 genomes/ml 159. However recent doubts have been expressed as to the reliability of the bDNA assay, as the sensitivity seems to vary according to genotype.

4.7.6 In the meta-analysis[125], the predictive value of low HCV RNA level for a sustained response was 51%, with an accuracy of 68%. Thus level of viraemia may be an important pre-treatment variable, but better and more reliable methods and studies are needed before this can be used in the decision making process.

4.7.7 Sequence analysis of the E2/NS1 region of HCV by analysing multiple clones from different patients has shown that the degree of variability in this region correlates with response to IFN[160] [161]. Responders show little or no sequence diversity in this region compared to non-responders who seem to be infected with a large heterogeneous pool of HCV variants. Viral heterogeneity may reflect higher replication rate, longer duration of infection, heterogeneous infecting inoculum or differential host immune responses. Most recently a so-called interferon sensitivity determining region (ISDR) has been described within the NS-5 region of the virus[162].

4.7.8 Similar pre-treatment factors have been analysed in the more recent combination treatment trials (see tables 2 and 3). In Poynard's IFN/Ribavirin combination study144 logistic regression revealed 5 factors associated with a favourable response: genotype 2 or 3, viral load less than 2 million copies per ml, age less than 40 years, minimal fibrosis on biopsy and female sex. Although the difference between 24 or 48 weeks combination treatment barely reached significance in McHutchinson's trial, it seems that those patients with factors associated with poor response such as genotype 1 and high level viraemia will benefit most from 48 weeks treatment. In patients infected with genotype 1 the sustained response rate increased from 16% for 24 weeks to 28% for 48 weeks treatment. In those patients infected with other genotypes the response rates were equally good for 24 (69%) and 48 (66%) weeks treatment. Similar findings were shown when patients were discriminated by HCV viraemia with improved sustained response rates for 48 weeks treatment (36%) in high level viraemia (2 million copies per ml) compared to 24 weeks (27%). In patients with low level viraemia there was no benefit in prolonging treatment to 12 months (24 weeks treatment - 42%; 48 weeks treatment - 43%).

- Treatment should not be withheld on the basis of genotype analysis or the measurement of HCV RNA levels (B).

- The duration of combination depends of the genotype and level of viraemia (A).

- Patients infected with non-HCV 1 (mostly genotype 2 or 3) should be treated for 6 months irrespective of the level of viraemia (A).

- Patients infected with genotype 1 and low level viraemia (< 2 million copies per ml) should be treated for 6 months whereas 12 months treatment is recommended for those infected with genotype 1 and high level viraemia (2 million copies per ml) (A). If HCV quantitation is not available treatment is recommended for 12 months in HCV 1 infected patients (A).

Predictors of response during treatment

4.7.9 The early period of treatment has also been studied to see if sustained response can be predicted. Early normalisation of ALT is a more accurate predictor of response to IFN monotherapy than any of the pre-treatment factors studied above. In a study of alfa-2b interferon Lindsay et al showed that no patient treated with 3MU who had not responded biochemically by week 12 responded subsequently to further treatment with IFN163. However a small percentage (12%) of these patients responded to high dose IFN (10MU) but their responses were not maintained.

4.7.10 Loss of HCV RNA during the initial weeks of treatment may also help predict response. In one study a positive PCR test at 3 months reliably predicted failure to demonstrate sustained response but a negative PCR at 3 months was not an accurate predictor[117]. A recent study suggests that loss of HCV RNA and normalisation of ALT are similar in their ability to predict response164. Further studies are needed to clarify the role of PCR testing at 3 months in determining whether to continue treatment. Future studies will also study the decline in viral load as a predictor.

4.7.11 Using the early treatment response is more accurate than pre-treatment assessment (other than the finding of cirrhosis) and many clinicians will stop treatment or consider other treatment options for those patients failing to normalise ALT's or who remain PCR positive at a defined point in treatment, such as at 3 months. This is a reasonable approach and will prevent excess costs of continuing IFN for a further 9 months in patients unlikely to derive biochemical or virological sustained response. One interesting finding from the combination treatment study by McHutchinson et al[145] was that in at least 50% of patients with a sustained response after initial treatment with combination therapy, HCV RNA was not cleared from serum until after week 12 or 24 of treatment. The reccomendation that early virological response should be used to determine further therapy needs to be evaluated in future studies of combination treatment.

- Patients unlikely to respond to IFN monotherapy can be identified at 3 months by persistent elevation of serum transaminase levels and the persisting presence of HCV RNA by PCR in serum (B).

- If ALT levels are normal or HCV RNA negative (or both) at 3 months, IFN monotherapy should be continued for the full duration (12 months) (B). In patients with initially normal ALT levels, failure to become RNA negative at 3 months suggests longer treatment will be ineffective (B).

- The recommendation that early treatment response can be used to predict sustained response does not apply to patients receiving combination therapy (A). In those patients receiving 12 months IFN/Ribavirin combination therapy a positive PCR at 6 months is an indication to stop treatment (C).

4.8 Side effects of treatment

Minor side effects

4.8.1 The majority of patients receiving IFN will report at least one side effect. Most of these are minor and do not require dose modification. The most common are flu-like symptoms including fatigue, headache, myalgia, fever, rigors and arthralgias. These effects occur 6-8 hours after the initial injection and can be ameliorated by taking paracetomol and by dosing at night before going to bed. Often these symptoms will improve after 2-4 weeks of treatment. Ribavirin may cause non-specific symptoms of fatigue, depression, insomnia and nausea.

4.8.2 Roughly 50% of patients taking IFN will report central nervous system symptoms such as irritability, depression, impaired concentration and insomnia. Other symptoms such as gastrointestinal complaints, alopecia and rhinorrhoea may occur.

4.8.3 Interferon has myelosuppressive effects resulting in reduced granulocyte, platelet and red cell counts. The reductions are usually mild and well tolerated unless there are existing haematological problems or evidence of hypersplenism and blood counts will return to normal after therapy. Increased triglyceride levels are commonly found as is mild proteinuria, both normalising after therapy.

Serious side effects

4.8.4 Serious neuropsychiatric side effects to IFN can occur and include depression, paranoia, severe anxiety and psychosis. In patients with a history of substance abuse, the psychiatric changes can lead to a disastrous relapse in alcohol or drug abuse. In some patients there is a deterioration in liver function, in some cases it can be severe, which may be due to the induction of an autoimmune hepatitis. These patients may have been mis-diagnosed or may have an underlying autoimmune diathesis. Autoantibodies such as antinuclear antibody (ANA), smooth muscle antibody (SMA) and liver kidney microsomal (LKM) should be screened for before therapy. The development of an immune hepatitis prompts withdrawal of IFN treatment.

4.8.5 Interferon therapy can lead to the development of several types of auto-antibody including anti-thyroid, antinuclear and antibodies against insulin. These are usually of no significance but the development of clinical autoimmune disease, such as thyroid disease, may lead to treatment withdrawal. Other reported conditions prompted by IFN include diabetes, thrombocytopenia, haemolytic anaemia, psoriasis, vitiligo, rheumatoid arthritis, SLE - like syndromes, primary biliary cirrhosis and sarcoidosis.

4.8.6 Renal lesions such as interstitial nephritis, nephrotic syndrome and acute renal failure have been described as have cardiovascular complications including arrhythmia's, ischaemic heart disease and cardiomyopathy. Retinopathy, hearing loss and severe pneumonitis have also been reported.

4.8.7 Overall the prevalence of serious side-effects is fairly low but there seems to be a dose-dependent increase in most. In Poynard's meta-analysis many common side-effects were far commoner in patients given high dose IFN (5MU) when compared to 3MU and led to dose reduction in 22% compared to 9% of patients. However the numbers of patients stopping treatment was similar (5% versus 4%)[125]. Serious or life-threatening side-effects occurred in 1-2% of patients.

4.8.8 The major adverse effect of Ribavirin is haemolysis. In Reichard's combination study side-effects were more common in the combination therapy group and prompted withdrawal of therapy in 7/50 combination therapy patients compared to 3/50 in the Interferon alone group[143]. In the French study[144] discontinuation of therapy for adverse events was more frequent with combination (19%) and monotherapy (13%) given for 48 weeks than combination given for 24 weeks (8%). In McHutchinson's trial the drug dose had to be reduced and treatment discontinued more often in patients treated with combination therapy; 8% (24 week) and 21% (48 week) discontinued for combination group, compared to 9% and 14% for the IFN monotherapy group. More frequent side effects are a potentially limiting factor to combination therapy.

- Although transient or mild side-effects are common during IFN monotherapy, serious toxicity requiring reduction in dose or cessation of treatment occurs in 5-10% of patients during treatment (A).

- Withdrawal from IFN/Ribavirin combination therapy occurs more often with 10-20% of patients requiring a reduction in dose or cessation of combination therapy (A).

4.9 Recommended Treatment Regime and Monitoring

4.9.1 Monitoring patients during therapy is extremely important, requiring regular clinical examination, psychological assessment, urinanalysis, serum chemistry, blood counts and thyroid function tests. Pregnancy tests should be performed prior to treatment and patients advised to not to conceive whilst on treatment and for at least 6 months after combination therapy.

4.9.2 We recommended using alpha interferon 3 MU three times per week for 12 months if used as monotherapy. Patients should be tested at 3 months and those failing to respond (biochemically and virologically) should stop therapy and be considered for further treatment trials of combination therapies. Combination therapy should be prescribed as IFN 3MU three times per week with Ribavirin 1000mg/day for patients weighing 75kg or less and 1200mg for those

weighing more than 75kg. Treatment should not be stopped at 3 months irrespective of biochemical or virological response but in those patients with treatment planned for 12 months (genotype 1) persistence of viraemia at 6 months may prompt treatment cessation.

4.9.3 Patients should be seen weekly for the first 4 weeks of IFN/Ribavirin combination treatment so that blood counts are performed to look for haemolysis. Thereafter patients should be seen at monthly intervals until 6 months and then 3 monthly until therapy is finished if treatment is given for a full year. Patients need continued support and encouragement and side-effects must be monitored. At each visit full blood counts, renal, thyroid and liver function tests should be taken. Serum for PCR should be taken at 3 months of treatment and if possible at every 3 months of therapy. In patients treated with IFN monotherapy a positive PCR test of serum at 3 months should prompt treatment withdrawal. The response to combination therapy should be assessed by PCR testing at 6 months in patients with genotype 1, treatment should be stopped if the PCR remains positive.

4.9.4 Dose reductions may be necessary for side-effects but if possible the course of IFN or IFN/Ribavirin should be completed. Follow-up testing, with serum ALT and serum RNA, should be performed 6 and 12 months after treatment. A negative PCR test 24 weeks after treatment cessation defines a sustained treatment response and in the majority of cases will remain negative in prolonged follow-up. We do not recommend routine follow-up liver biopsy.

4.10 Treatment of Non-Responders and Relapsers after IFN Monotherapy

4.10.1 The response rate for a second course of IFN is extremely poor in patients failing to respond to an initial course of IFN (abnormal ALT at the end of therapy). In a review of 13 studies including 591 non-responders, the sustained response rates to a second course were 1-3%[165].

4.10.2 However the results of a second course of IFN in patients relapsing after therapy are more encouraging. The rates of sustained response were 15% for patients receiving a second course of 3MU for 6 months, 29% in patients receiving 3MU for 6 months and as high as 43% in patients treated for 12 months or longer. In studies that analysed virological response, the presence of a negative PCR test at the end of the first course of treatment was highly predictive of a sustained response after re-treatment. The combined analysis of 5 studies showed a sustained response in 56% of 145 patients rendered PCR negative at the end of first course of treatment compared to 2.9% of 206 who remained PCR positive but with normal ALT levels at the end of first course of therapy[165]. There appears little point in re-treating patients who relapse after an initial high dose IFN course as sustained response rates are low (<5%).

4.10.3 More recently IFN/Ribavirin combination studies have also revealed improved response rates for a further course of combination therapy after either a failed course of IFN monotherapy or in patients who relapse after treatment. In an Italian study of 96 non-responders, HCV RNA was undetectable at the end of treatment in 27% of patients treated with a further 6 month course of combination therapy compared to 7% in those treated with IFN monotherapy ($p<0.05$)[166]. However at 6 months after therapy the response rate had fallen to 15%. In a Spanish study the 6 month post therapy response was 10% for a mixed group of non-responders and relapsers[167]. In another study with equal numbers of non-responders (24) and relapsers (24), HCV was not detectable 6 months after treatment in 20.8% of those treated with combination therapy compared to 4.2% treated with a further course of IFN monotherapy[168]. However in this study 25% of patients required dose reduction and 12.5% of patients were withdrawn due to intolerable side-effects.

4.10.4 The International Hepatitis Interventional Therapy Group published their randomised study of 345 relapsers treated with a further 6 month course of IFN/Ribavirin or IFN monotherapy[169]. The primary end-point was the absence of HCV RNA in serum at the end of therapy and 6 months after the cessation of therapy. At the end of treatment 82% (141/173) vs 47% (80/172) were PCR negative for the combination versus monotherapy groups respectively ($p<0.001$). At 6 months after treatment cessation the rates of PCR negativity were 49% vs 5% ($p<0.001$). In this study the safety profiles of the two treatment regimes were similar with discontinuation of therapy in 6% of the combination group and 3% of the IFN monotherapy group.

- Patients with a combined biochemical and virological response at the end of IFN monotherapy, who relapse in follow-up over the next year, have a significant chance of a sustained response after further treatment with IFN/Ribavirin and (A).

- Patients with a biochemical but not virological response during initial treatment with IFN monotherapy are unlikely to have a sustained response to further treatment with IFN/Ribavirin (A).

4.11 Cost-Effective Analysis

4.11.1 The long term benefit of antiviral therapy is difficult to prove currently due to the relatively long natural history of HCV and the fact that patients need to be followed up for many years after successful viral eradication. So far studies have shown that sustained viral response (i.e. negative PCR at 24 weeks after treatment cessation) is maintained for several years and that these viral responses are accompanied by improvements in histological scores of necroinflammation. It seems reasonable to suggest that sustained virological responders will derive long term benefit and will not progress to end-stage liver disease as frequently as those failing to respond. Those studies showing reduced rates of hepatocellular carcinoma in treated patients support this view although the results of further studies are needed to clarify this issue. Whilst monitoring and treating patients costs money, far greater health care related costs are incurred when patients develop cirrhosis and its complications including variceal bleeding or the development of hepatocellular carcinoma[170]. However disease progression is not universal and treatment may be unnecessary in patients who do not develop HCV related complications in their lifetime.

4.11.2 Treatment with IFN and Ribavirin is associated with high initial costs, and studies need to address the relative cost-effectiveness of treatment in terms of years of life gained, quality of life, indirect costs including loss of productivity for sick patients and projected health care costs for the management of the complications of chronic HCV such as the development of cirrhosis and hepatocellular carcinoma.

4.11.3 The costs of implementing a management policy involve staff, laboratory and drug costs. Patients attending clinics regularly will use medical, nursing, secretarial and other staff time, although many will attend general medical or perhaps gastroenterological/hepatological clinics. In larger centres there may be specialist clinics with attending clinical nurse specialists. The laboratory costs will include routine blood testing, analysis of liver biopsy specimens and PCR testing (cost~£40-50). The cost of 1 year's IFN at 3MU three times weekly is roughly £3,000 rising to £6,000 for six months combination therapy and £12,000 for those requiring 12 months of IFN/Ribavirin combination treatment.

4.11.4 Economic analysis must play a part in planning the management of HCV, but due to the long course of the disease many of the important questions about cost-effectiveness of therapy cannot be answered. Instead researchers have made use of modelling using Markov simulations to predict the likely outcomes and thus assess the impact of therapy, such as the one produced by Dusheiko and Roberts[171]. This model analysed two hypothetical groups of patients, one treated and one untreated, followed for 30 years. The costs estimated were only those direct costs associated with hospital follow-up and treatment, and those indirect costs including quality of life, time off work and so on were not assessed. Thus the value of intervention in this model was underestimated.

4.11.5 Not surprisingly the costs in the treated group were higher in the first year while treatment is given and follow-up is intense. However in subsequent years the costs in the treated cohort were less than the untreated group because fewer entered the later expensive stages of the disease. Although IFN monotherapy is expensive it is not out of line with many other health care interventions with a discounted cost per year of life saved ranging from £2,142 to £8,555. This compares to figures of £32,000 for cholesterol reduction in patients with coronary heart disease[172], £6,315 for home dialysis[173] and £3,135 for enalapril treatment of chronic heart failure[174].

4.11.6 The model was based on information available in the early 1990's and as more data becomes available about response to treatment and pathogenicity of the various groups it should be possible to produce models that more accurately reflect disease patterns. Wong et al have assessed the cost effectiveness of IFN/Ribavirin combination versus IFN monotherapy using recent controlled trial data[175]. In comparison with 12 month IFN monotherapy, the model indicated that combination therapy for 6 or 12 months should increase life expextancy and is cost effective with a marginal cost-effectiveness ratio of $2,100 and $2,300 per discounted quality-adjusted life-year gained, respectively. The Scottish Health Purchasing Information Centre have developed a spreadsheet that can be used to estimate costs and is available from the group[176]. Their cost per life year saved estimates were £3,000 (1000mg Ribavirin) and £3,500 (1200mg Ribavirin) for 6 months and £6,000 and £6,700 for 12 months when compared to no treatment. Once again these figures are within the range of other accepted NHS activities. Any increase in targeting therapy to particular groups, such as genotypes, must be balanced with the costs of screening procedures and the sensitivity and specificity of these procedures. Later delivery of therapy to a group of progressors is likely to be more cost-effective, as the benefits are likely to be felt sooner.

4.11.7 More information is needed and the results of future studies should include indirect costs to patients, primary care and community services, and improved outcome measures such as quality of life measures should be incorporated into the analysis.

5.0 Future Research

5.1.1 There is a pressing need for further research into several important areas of HCV infection. The most important areas of future research are: the determination of the natural history of HCV infection in the UK with the study of the cohort identified in the "lookback study", multivariate analysis of current data to analyse factors predictive of response to treatment, the development of new antiviral therapies, prolonged follow-up of those patients already treated in trials to determine the long term improvements in terms of liver disease progression and finally determining whether screening for HCC is beneficial in the HCV infected patient population. Future research will also focus on the development of more effective and better tolerated therapies such as pegylated interferon and also on the development of treatment in special situations such as acute HCV, mild hepatitis and in advanced liver disease.

Appendix 1

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Table 1. Sustained virological responses (SR - PCR negative 24 weeks after treatment cessation) in naive patients taken from the two multicentre randomised controlled trials published in 1998[144] [145]

Treatment duration	SR IFN/placebo 24 weeks	SR IFN/placebo 48 weeks	SR IFN/Ribavirin 24 weeks	SR IFN/Ribavirin 48 weeks
Poynard 832 patients	-	53/278 19%	96/277 35%	118/277 43%
McHutchinson 681 patients	13/231 6%	29/225 13%	70/228 31%	87/228 38%
Total = 1513	13/231 6%	82/503 16%	166/505 33%	205/505 41%

Table 2. Sustained responses (SR - PCR negative 24 weeks after treatment cessation) according to genotype in naive patients taken from the two multicentre randomised controlled trials published in 1998[144] [145]

Treatment duration	SR IFN/placebo 24 weeks	SR IFN/placebo 48 weeks	SR IFN/Ribavirin 24 weeks	SR IFN/Ribavirin 48 weeks
Poynard genotype 1 genotype non-1	 - -	 20/179 (11%) 33/99 (33%)	 32/177 (18%) 64/100 (64%)	 56/180 (31%) 62/97 (64%)
McHutchinson genotype 1 genotype non-1	 3/167 (2%) 10/64 (16%)	 11/162 (7%) 18/63 (29%)	 26/164 (16%) 44/64 (69%)	 46/166 (28%) 41/61 (66%)
Total genotype 1 genotype non-1	 3/167 (2%) 10/64 (16%)	 33/341 (10%) 51/162 (31%)	 58/341 (17%) 110/164 (67%)	 102/346 (29%) 103/158 (65%)

Table 3. Sustained responses (SR - PCR negative 24 weeks after treatment cessation) according to baseline viraemia (expressed as copies per ml) naive patients taken from the two multicentre randomised controlled trials published in 1998[144] [145]

Treatment duration	SR IFN/placebo 24 weeks	SR IFN/placebo 48 weeks	SR IFN/Ribavirin 24 weeks	SR IFN/Ribavirin 48 weeks
Poynard $2x10^6$ copies/ml $<2x10^6$ copies/ml	 - -	 24/183 (13%) 29/95 (31%)	 48/169 (28%) 48/108 (44%)	 64/162 (40%) 54/115 (47%)

McHutchinson $2x10^6$ copies/ml $<2x10^6$ copies/ml	6/157 (4%) 7/74 (9%)	11/162 (7%) 18/63 (29%)	44/166 (27%) 26/62 (42%)	54/152 (36%) 33/76 (43%)
Total $2x10^6$ copies/ml $<2x10^6$ copies/ml	6/157 (4%) 7/74 (9%)	35/345 (10%) 47/158 (30%)	92/335 (27%) 74/170 (44%)	118/314 (38%) 87/191 (46%)

Table 4. Sustained response (SR - PCR negative 24 weeks after treatment cessation) rates for cirrhotic patients (includes patients with bridging fibrosis - brid. fib.) compared to patients with minimal fibrosis taken from the study by McHutchinson et al[145]

Treatment duration	SR IFN/placebo 24 weeks	SR IFN/placebo 48 weeks	SR IFN/Ribavirin 24 weeks	SR IFN/Ribavirin 48 weeks
cirrhosis/brid. fib. minimal/no fibrosis	3/65 (5%) 7/154 (5%)	9/71 (13%) 18/136 (13%)	17/59 (29%) 51/159 (32%)	21/55 (38%) 62/159 (39%)

Disclaimer

This supplement has been published on the Gut website prior to appearing in print at the request of the British Society of Gastroenterology. The supplement will be available in print in June 2001. Minor modifications have been made to the text for style but it has **not** been edited for content.