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REVIEW

Is pegylated interferon superior to interferon, with ribavarin, in chronic hepatitis C genotypes 2/3?

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Abstract

Over the past decade, significant improvements have been made in the treatment of chronic hepatitis C (CHC), especially with the introduction of combined therapy using both interferon and ribavarin. The optimal dose and duration of treatment is still a matter of debate and, importantly, the efficacy of this combined treatment varies with the viral genotype responsible for infection. In general, patients infected with viral genotypes 2 or 3 more readily achieve a sustained viral response than those infected with viral genotype 1. The introduction of a pegylated version of interferon in the past decade has produced better clinical outcomes in patients infected with viral genotype 1. However, the published literature shows no improvement in clinical outcomes in patients infected with viral genotypes 2 or 3 when they are treated with pegylated interferon as opposed to non-pegylated interferon, both given in combination with ribavarin. This is significant because the cost of a 24-wk treatment with pegylated interferon in less-developed countries is between six and 30 times greater than that of treatment with interferon. Thus, clinicians need to carefully consider the cost-*versus*-benefit of using pegylated interferon to treat CHC, particularly when there is no evidence for clinically measurable benefits in patients with genotypes 2 and 3 infections.

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INTRODUCTION

The hepatitis C virus (HCV) is a non-cytopathic member of the Flaviviridae family that causes acute and chronic hepatitis and can lead to the development of hepatocellular carcinoma (HCC). An estimated 3% of the world's population is infected with HCV[1]. Acute infection is usually asymptomatic, which makes early diagnosis difficult. A distinct feature of HCV infection is its proclivity towards becoming chronic in as many as 70% of acute infections. Importantly, chronic hepatitis C (CHC) is associated with the progressive development of fibrosis and cirrhosis that, if left untreated, can lead to end-stage liver disease with an estimated 5%-20% mortality rate.

PREVALENCE AND VIRAL GENOTYPE

Preliminary surveys from Pakistan suggest that the seroprevalence of HCV is > 5%, while other surveys suggest rates as high as 10%[2-6]. In one study[7] of prospective blood donors in Faisalabad, Pakistan, 78/294 individuals or 26.5% were found to be seropositive for HCV. If representative, this would be appreciably greater by far than the prevalence rate of 2.9% estimated for Egypt, a country with one of the highest HCV infection rates[8].

The predominant form of HCV infections in Pakistan is of the genotype 3 variety, and this genotype is also predominant in northern, northeastern, and central India, with infection rates as high as 71% in acute

hepatitis patients, and as high as 82% in chronic hepatitis patients[9,10]. From a global public health perspective, sizeable fractions of CHC populations outside southern Asia are also infected with viral genotypes 2 and 3. For example, 26.9% of CHC patients in Serbia and Montenegro have been reported to be infected with genotypes 2 or 3[11]. An estimated 37% of 90 consecutive liver patients from Novara, Italy, had genotype 2[12]. In Cordoba, Argentina, 55% of 96 consecutive liver patients had genotype 2 and 5% had genotype 3[13]. An estimated HCV prevalence of 31% for genotype 3 and 4.3% for genotype 2 has been reported in Brazil[14]. These data from the more densely populated areas of the world suggest that the actual number of people infected with either genotype 2 or 3 is quite substantial compared to those with genotype 1, the predominant form in North America and northern Europe, although an estimated 16% of CHC patients in the United States are also infected with genotypes 2 or 3, as compared to 72% with genotype 1 (http://www.hepatitis.va.gov/vahep?page=diag-tests-03-05).

TREATMENT OPTIONS AND CLINICAL OUTCOMES

In the past two decades, considerable progress has been made in the treatment of this disease with the introduction of interferon (IFN), and, subsequently, with the addition of the guanosine analogue, ribavarin (RBV), in 1998. Typically, patients are treated with IFN by subcutaneous injection three times per week in conjunction with a daily oral dose of RBV (800-1200 mg/day, adjusted by body weight) for between 24 and 48 wk. The therapeutic efficacy is typically measured by the following end points: (1) a sustained virologic response (SVR), defined as no detectable levels of the viral RNA in serum at least 24 wk after the end of treatment; (2) a decrease in the liver enzyme, alanine aminotransferase (ALT) to within the normal reference range; and (3) signs of histological improvement as demonstrated typically by a paired liver biopsy performed prior to the initiation of therapy and at 24 wk after the end of therapy.

Correlations between serum virus levels, serum ALT levels, and liver pathology, while generally acceptable[15,16], have not been definitively established. The primary measure of current therapy is the achievement of virtually no detectable levels of HCV in serum at least 24 wk following the end of therapy, defined as the SVR. The SVR correlates well in clinical practice with patient recovery and wellbeing.

In the past decade, it has been reported that the addition of a polyethylene glycol (Peg) moiety to IFN (termed, Peg-IFN) significantly enhances its half-life in the blood, such that patients can be dosed with the Peg-IFN once weekly as compared to three times a week for the non-pegylated IFN.

In a study[17] of 531 CHC patients (190 of whom were HCV genotype 2 or 3, and 329 were genotype 1), treated with Peg-IFN or IFN, without RBV, for 48 wk and followed up for an additional 24 wk, the overall SVR at 72 wk was 39% (95% CI, 33%-45%) for Peg-IFN and 19% (95% CI, 14%-24%) for IFN. The data were not separated by genotype. The authors noted that the rate of relapse between weeks 48 and 72 was higher among patients who had a response to Peg-IFN compared to those treated with IFN. In a randomized double-blind study[18] of 1219 patients treated with Peg-IFN alone compared to IFN, both administered without RBV, significant improvements, including SVR, were noted in patients with genotype 1 virus, with a trend towards an improved, although not significant, response in patients with genotypes 2 and 3.

Treatment of CHC patients with Peg-IFN + RBV (the RBV dose typically weight-based but sometimes flat-dosed between 800 and 1200 mg/day, per os) has been shown to result in appreciably better clinical outcomes and has been touted as the so-called gold standard in the treatment of CHC. This conclusion stems almost exclusively from two studies[19,20] in which CHC patients were treated with Peg-IFN + RBV or with IFN + RBV. The data from these two studies have shown that the single greatest advantage of the Peg-IFN over IFN, both given in combination with RBV, has been the achievement of a statistically significant SVR in CHC patients with genotype 1, the recalcitrant form of this viral disease. The studies showed no consistent advantage of Peg-IFN over IFN (either one given in combination with RBV) in patients with viral genotypes 2 or 3. In the Manns *et al* study[19], the SVR was 76% for genotypes 2 or 3 and ranged from 36 to 56% in genotype 1 patients treated with IFN + RBV or Peg-IFN + RBV. In a randomized study of 1311 CHC patients given only Peg-IFN + RBV, Hadziyannis *et al*[21] reported an SVR of approximately 80% in those infected with genotype 2 or 3 virus *versus* approximately 52% in those with genotype 1 virus. Several other studies[22-38] of CHC patients with genotype 2 or 3 virus, treated with either Peg-IFN or IFN, both administered with RBV, are summarized in Table 1 and show no better results with either IFN, when given in combination with RBV, for genotypes 2 and 3 viruses.

Notwithstanding the published clinical data[19-38] summarized in Table 1, the debate on the optimal duration of Peg-IFN treatment with RBV continues. In a recent paper, Shiffman *et al*[34] have suggested that it may be prudent to treat CHC patients with genotype 2 or 3 virus for 24 wk as opposed to 16 wk, to ensure a lower percentage of relapses. The concept of an early virological response, sometimes referred to as a rapid viral response (RVR), reported in some fraction of CHC patients within 4 wk, has been proposed as a clinically useful predictor of SVR[39]. However, while this concept is valuable in CHC patients infected with genotype 1 or 4 virus, some 97% of patients with genotypes 2 and 3 viruses show an RVR, and therefore, this concept is less useful in CHC patients infected with genotype 2 or 3[40]. Importantly, the rates of relapse can increase with therapies of shorter duration, although

Table 1 Achievement of SVR by treatment with IFN + RBV or Peg-IFN + RBV in CHC patients

No. of patients	IFN + RBV	Peg-IFN + RBV	HCV genotype	Reference
446	79	81%	2/3	Manns *et al*[19]
214	61	76%	2/3	Fried *et al*[20]
492	NT	74-88	2/3	Hadziyannis *et al*[21]
253	66	NT	2/3	McHutchinson *et al*[22]
75	73	NT	non-1	Davis *et al*[23]
100	79.5	NT	3	Khokar[24]
350	85	NT	3	Muhammad *et al*[25]
20	95	NT	3	Hazari *et al*[26]
283	NT	80	2	Mangia *et al*[27]
	NT	66	3	Mangia *et al*[27]
18	72	NT	3	Medeiros-Filho *et al*[28]
28	NT	78	2/3	Gupta *et al*[29]
142	NT	81.7	2/3	Elefsiniotis *et al*[30]
1552	NT	75.6-79.2	2/3	Jacobson *et al*[31]
397	NT	83.6	2/3	Borroni *et al*[32]
230	82	78	2	Rumi *et al*[33]
356	NT	75	2	Shiffman *et al*[34]
369	NT	66	3	Shiffman *et al*[34]
285	NT	86.3-93.2	2/3	Dalgard *et al*[35]
82	73	87	2/3	Poustchi *et al*[36]
51	66.7	NT	2	Kawamura *et al*[37]
141	NT	67.5-77.8	2/3	Ferenci *et al*[38]

NT: Not tested.

the SVR rates (27.8% and 58.8%) were inexplicably low in one particular study of genotype 3 CHC patients in Pakistan[41].

Emerging data[27,30,32,38-40] suggest differences in SVR between patients with genotype 2 or 3 HCV, with genotype 2 yielding better responses than 3. There may also be additional nuances between genotypes 2a and 2c that could be used to the benefit of patients with these sub-types of HCV infection.

NEWER SUPPLEMENTAL TREATMENT OPTIONS TO INCREASE THERAPEUTIC EFFICACY AND PREVENT RELAPSE

Two new adjuvants to existing therapies with IFN + RBV or Peg-IFN + RBV are noteworthy in their potential to vastly improve SVR and clinical outcomes, and importantly, to decrease relapse rates in CHC patients. While abnormalities in glucose metabolism in CHC patients were recognized as far back as 1994[42], the application of this knowledge in the clinical setting has been introduced in just the past few years, as the epidemic of obesity and pre-diabetes or diabetes has come into sharp focus as a matter of great public health concern.

Eighty-two CHC patients[36] with genotype 2 or 3 virus were treated with IFN + RBV or Peg-IFN + RBV. Insulin resistance was measured by the homeostasis model (HOMA-IR). Patients with HOMA-IR values < 2 had an SVR of 94%, those with HOMA-IR values of 2-4 or > 4 had an SVR of 65%. The authors concluded that SVR rates > 90% are achievable in persons with low HOMA-IR values in genotype 2 and 3 patients, but drop to the 60% level more typically seen in CHC genotype 1 patients when their HOMA-IR values are > 2. Similar results have been reported more recently by others[43-46].

In an elegant series of papers from the Siddiqui Laboratory at the University of California at San Diego, *in vitro* studies on the mechanisms of HCV-induced changes in liver cells have identified the importance of intracellular calcium and oxidative stress in activating signal transducer and activator of transcription and nuclear factor-κB which in turn, contribute to the release of pro-inflammatory cytokines and contribute to liver pathology in HCV-infected cells[47-51]. This mechanism has been confirmed by others[52,53] and summarized in a recent review, in the context of immune system derangements observed in CHC[54].

We are in the early stages of designing a pilot study to evaluate the effectiveness of drugs, such as exenatide, used to overcome insulin resistance and agents that would block calcium derangements in the liver of CHC patients infected with HCV genotype 2 or 3.

CONCLUSION

Published and unpublished clinical observations suggest that an SVR is achieved in 70%-88% of CHC patients infected with genotype 2 or 3 HCV treated with IFN + RBV. A weight-of-evidence analysis using the data cited in Table 1, suggests no greater benefit in treating genotype 2 or 3 infections with Peg-IFN, which can be as much as six to 30 times more expensive than IFN (unpublished data). While the number of patients studied (Table 1) may be smaller than optimally required for a definitive answer to the issue of whether Peg-IFN, despite its additional costs, brings any clinical benefit to CHC patients with genotype 2 or 3 infection, the similarities in SVR between the two IFNs suggest that neither offers a measurable clinical benefit over the other when administered with RBV.

The 2002 National Institutes of Health (NIH) Consensus Conference Statement[55] on Management of Hepatitis C stated, "Among patients with genotypes 2 or 3, SVRs with standard interferon and ribavarin were comparable to those with pegylated interferon and ribavarin, and thus standard interferon and ribavarin could be used in treating patients with those genotypes". The published data since the 2002 NIH Consensus Statement have not falsified this recommendation. Thus, the recommendation of duration of Peg-IFN therapy for hepatitis C with these genotypes needs to be tempered by whether or not Peg-IFN offers any clinical advantage, given its much higher cost, when used with RBV, and especially in less-developed countries.

REFERENCES

1 **Weiss U**. Hepatitis C. *Nature* 2005; **436**: 929
2 **Malik IA**, Ahmad N, Luqman M, Legters LJ, Khalil-Ullah, Zaheeruddin, Ahmed A, Bukhtiari N, Nabi S, Mubarik A. Hepatitis C as a cause of chronic liver disease in northern Pakistan. *J Pak Med Assoc* 1992; **42**: 67-68
3 **Aslam M**, Aslam J. Seroprevalence of the antibody to hepatitis C in select groups in the Punjab region of Pakistan.

J Clin Gastroenterol 2001; **33**: 407-411
4 **Khan TS**, Rizvi F, Rashid A. Hepatitis C seropositivity among chronic liver disease patients in Hazara, Pakistan. *J Ayub Med Coll Abbottabad* 2003; **15**: 53-55
5 **Khokhar N**, Gill ML, Malik GJ. General seroprevalence of hepatitis C and hepatitis B virus infections in population. *J Coll Physicians Surg Pak* 2004; **14**: 534-536
6 **Muhammad N**, Jan MA. Frequency of hepatitis "C" in Buner, NWFP. *J Coll Physicians Surg Pak* 2005; **15**: 11-14
7 **Ahmad N**, Asgher M, Shafique M, Qureshi JA. An evidence of high prevalence of Hepatitis C virus in Faisalabad, Pakistan. *Saudi Med J* 2007; **28**: 390-395
8 **Alter MJ**. Epidemiology of hepatitis C virus infection. *World J Gastroenterol* 2007; **13**: 2436-2441
9 **Chaudhuri S**, Das S, Chowdhury A, Santra A, Bhattacharya SK, Naik TN. Molecular epidemiology of HCV infection among acute and chronic liver disease patients in Kolkata, India. *J Clin Virol* 2005; **32**: 38-46
10 **Hissar SS**, Goyal A, Kumar M, Pandey C, Suneetha PV, Sood A, Midha V, Sakhuja P, Malhotra V, Sarin SK. Hepatitis C virus genotype 3 predominates in North and Central India and is associated with significant histopathologic liver disease. *J Med Virol* 2006; **78**: 452-458
11 **Svirtlih N**, Delic D, Simonovic J, Jevtovic D, Dokic L, Gvozdenovic E, Boricic I, Terzic D, Pavic S, Neskovic G, Zerjav S, Urban V. Hepatitis C virus genotypes in Serbia and Montenegro: the prevalence and clinical significance. *World J Gastroenterol* 2007; **13**: 355-360
12 **Sartori M**, Andorno S, Avogadro E, Ballare M, La Terra G, Leone F, Quaglia V, Fortina G, Aglietta M. High prevalence of hepatitis C virus (HCV) genotype 2 in Italian patients with chronic liver disease. *Ital J Gastroenterol* 1996; **28**: 452-456
13 **Re V**, Lampe E, Yoshida CF, de Oliveira JM, Lewis-Ximinez L, Spinsanti L, Elbarcha O, Contigiani M. Hepatitis C virus genotypes in Cordoba, Argentina. Unexpected high prevalence of genotype 2. *Medicina* (B Aires) 2003; **63**: 205-210
14 **Bassit L**, Ribeiro-Dos-Santos G, Da Silva LC, Takei K, Villaca P, David-Neto E, Chamone D, Saez-Alquezar A. Genotype distributions of hepatitis C virus in Sao Paulo, Brazil: rare subtype found. *Hepatology* 1999; **29**: 994-995
15 **Patel K**, McHutchison JG. Initial treatment for chronic hepatitis C: current therapies and their optimal dosing and duration. *Cleve Clin J Med* 2004; **71** Suppl 3: S8-S12
16 **Saleem N**, Mubarik A, Qureshi AH, Siddiq M, Ahmad M, Afzal S, Hussain AB, Hashmi SN. Is there a correlation between degree of viremia and liver histology in chronic hepatitis C? *J Pak Med Assoc* 2004; **54**: 476-479
17 **Zeuzem S**, Feinman SV, Rasenack J, Heathcote EJ, Lai MY, Gane E, O'Grady J, Reichen J, Diago M, Lin A, Hoffman J, Brunda MJ. Peginterferon alfa-2a in patients with chronic hepatitis C. *N Engl J Med* 2000; **343**: 1666-1672
18 **Lindsay KL**, Trepo C, Heintges T, Shiffman ML, Gordon SC, Hoefs JC, Schiff ER, Goodman ZD, Laughlin M, Yao R, Albrecht JK. A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. *Hepatology* 2001; **34**: 395-403
19 **Manns MP**, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358**: 958-965
20 **Fried MW**, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr, Haussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; **347**: 975-982
21 **Hadziyannis SJ**, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H Jr, Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A, Ackrill AM. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; **140**: 346-355
22 **McHutchison JG**, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, Goodman ZD, Ling MH, Cort S, Albrecht JK. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. *N Engl J Med* 1998; **339**: 1485-1492
23 **Davis GL**, Esteban-Mur R, Rustgi V, Hoefs J, Gordon SC, Trepo C, Shiffman ML, Zeuzem S, Craxi A, Ling MH, Albrecht J. Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. International Hepatitis Interventional Therapy Group. *N Engl J Med* 1998; **339**: 1493-1499
24 **Khokhar N**. Effectiveness of 48 weeks Interferon alfa-2b in combination with ribavirin as initial treatment of chronic hepatitis. *J Ayub Med Coll Abbottabad* 2002; **14**: 5-8
25 **Muhammad N**, Jan MA, Rahman N. Outcome of combined interferon-ribavirin in the treatment of chronic hepatitis C. *J Coll Physicians Surg Pak* 2004; **14**: 651-653
26 **Hazari S**, Panda SK, Gupta SD, Batra Y, Singh R, Acharya SK. Treatment of hepatitis C virus infection in patients of northern India. *J Gastroenterol Hepatol* 2004; **19**: 1058-1065
27 **Mangia A**, Santoro R, Minerva N, Ricci GL, Carretta V, Persico M, Vinelli F, Scotto G, Bacca D, Annese M, Romano M, Zechini F, Sogari F, Spirito F, Andriulli A. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2005; **352**: 2609-2617
28 **Medeiros-Filho JE**, de Carvalho Mello IM, Pinho JR, Neumann AU, de Mello Malta F, da Silva LC, Carrilho FJ. Differences in viral kinetics between genotypes 1 and 3 of hepatitis C virus and between cirrhotic and non-cirrhotic patients during antiviral therapy. *World J Gastroenterol* 2006; **12**: 7271-7277
29 **Gupta R**, Ramakrishna CH, Lakhtakia S, Tandan M, Banerjee R, Reddy DN. Efficacy of low dose peginterferon alpha-2b with ribavirin on chronic hepatitis C. *World J Gastroenterol* 2006; **12**: 5554-5556
30 **Elefsiniotis IS**, Pantazis KD, Dimitroulopoulos D, Koutsounas S, Moulakakis A, Paraskevas E. Impact of shorter duration of treatment on virological response rate in genotype 2 or 3 chronic hepatitis C virus infection. *Indian J Gastroenterol* 2007; **26**: 209-213
31 **Jacobson IM**, Brown RS Jr, Freilich B, Afdhal N, Kwo PY, Santoro J, Becker S, Wakil AE, Pound D, Godofsky E, Strauss R, Bernstein D, Flamm S, Pauly MP, Mukhopadhyay P, Griffel LH, Brass CA. Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. *Hepatology* 2007; **46**: 971-981
32 **Borroni G**, Andreoletti M, Casiraghi MA, Ceriani R, Guerzoni P, Omazzi B, Terreni N, Salerno F. Effectiveness of pegylated interferon/ribavirin combination in 'real world' patients with chronic hepatitis C virus infection. *Aliment Pharmacol Ther* 2008; **27**: 790-797
33 **Rumi MG**, Aghemo A, D'Ambrosio R, Ronchi G, Del Ninno E, Gallus S, Colombo M. Lack of rapid virological response predicts interferon-alpha2b/ribavirin therapy failure in HCV genotype 2 patients: a single-centre study. *Antivir Ther* 2007; **12**: 1033-1040
34 **Shiffman ML**, Suter F, Bacon BR, Nelson D, Harley H, Sola R, Shafran SD, Barange K, Lin A, Soman A, Zeuzem S. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2007; **357**: 124-134
35 **Dalgard O**, Bjoro K, Ring-Larsen H, Bjornsson E, Holberg-Petersen M, Skovlund E, Reichard O, Myrvang B, Sundelof B, Ritland S, Hellum K, Fryden A, Florholmen J, Verbaan H. Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. *Hepatology* 2008; **47**: 35-42

36 **Poustchi H**, Negro F, Hui J, Cua IH, Brandt LR, Kench JG, George J. Insulin resistance and response to therapy in patients infected with chronic hepatitis C virus genotypes 2 and 3. *J Hepatol* 2008; **48**: 28-34

37 **Kawamura Y**, Arase Y, Ikeda K, Suzuki F, Suzuki Y, Kobayashi M, Akuta N, Hosaka T, Sezaki H, Yatsuji H, Kobayashi M, Kumada H. The efficacy of short-term interferon-beta therapy for chronic hepatitis C patients with low virus load. *Intern Med* 2008; **47**: 355-360

38 **Ferenci P**, Brunner H, Laferl H, Scherzer TM, Maieron A, Strasser M, Fischer G, Hofer H, Bischof M, Stauber R, Gschwantler M, Steindl-Munda P, Staufer K, Loschenberger K. A randomized, prospective trial of ribavirin 400 mg/day versus 800 mg/day in combination with peginterferon alfa-2a in hepatitis C virus genotypes 2 and 3. *Hepatology* 2008; **47**: 1816-1823

39 **Yu ML**, Dai CY, Huang JF, Hou NJ, Lee LP, Hsieh MY, Chiu CF, Lin ZY, Chen SC, Hsieh MY, Wang LY, Chang WY, Chuang WL. A randomised study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. *Gut* 2007; **56**: 553-559

40 **Berg T**, Carosi G. Optimizing outcomes in patients with hepatitis C virus genotype 2 or 3. *Antivir Ther* 2008; **13** Suppl 1: 17-22

41 **Zuberi BF**, Zuberi FF, Memon SA, Qureshi MH, Ali SZ, Afsar S. Sustained virological response based on rapid virological response in genotype-3 chronic hepatitis C treated with standard interferon in the Pakistani population. *World J Gastroenterol* 2008; **14**: 2218-2221

42 **Ishigami Y**, Kanda T, Wada M, Shimizu Y. [Glucose intolerance during interferon therapy in patients with chronic hepatitis type C] *Nippon Rinsho* 1994; **52**: 1901-1904

43 **Simo R**, Lecube A, Genesca J, Esteban JI, Hernandez C. Sustained virological response correlates with reduction in the incidence of glucose abnormalities in patients with chronic hepatitis C virus infection. *Diabetes Care* 2006; **29**: 2462-2466

44 **Imazeki F**, Yokosuka O, Fukai K, Kanda T, Kojima H, Saisho H. Prevalence of diabetes mellitus and insulin resistance in patients with chronic hepatitis C: comparison with hepatitis B virus-infected and hepatitis C virus-cleared patients. *Liver Int* 2008; **28**: 355-362

45 **Harrison SA**. Insulin resistance among patients with chronic hepatitis C: etiology and impact on treatment. *Clin Gastroenterol Hepatol* 2008; **6**: 864-876

46 **Romero-Gomez M**, Fernandez-Rodriguez CM, Andrade RJ, Diago M, Alonso S, Planas R, Sola R, Pons JA, Salmeron J, Barcena R, Perez R, Carmona I, Duran S. Effect of sustained virological response to treatment on the incidence of abnormal glucose values in chronic hepatitis C. *J Hepatol* 2008; **48**: 721-727

47 **Gong G**, Waris G, Tanveer R, Siddiqui A. Human hepatitis C virus NS5A protein alters intracellular calcium levels, induces oxidative stress, and activates STAT-3 and NF-kappa B. *Proc Natl Acad Sci USA* 2001; **98**: 9599-9604

48 **Tardif KD**, Waris G, Siddiqui A. Hepatitis C virus, ER stress, and oxidative stress. *Trends Microbiol* 2005; **13**: 159-163

49 **Waris G**, Turkson J, Hassanein T, Siddiqui A. Hepatitis C virus (HCV) constitutively activates STAT-3 via oxidative stress: role of STAT-3 in HCV replication. *J Virol* 2005; **79**: 1569-1580

50 **Waris G**, Felmlee DJ, Negro F, Siddiqui A. Hepatitis C virus induces proteolytic cleavage of sterol regulatory element binding proteins and stimulates their phosphorylation via oxidative stress. *J Virol* 2007; **81**: 8122-8130

51 **Nasimuzzaman M**, Waris G, Mikolon D, Stupack DG, Siddiqui A. Hepatitis C virus stabilizes hypoxia-inducible factor 1alpha and stimulates the synthesis of vascular endothelial growth factor. *J Virol* 2007; **81**: 10249-10257

52 **Farinati F**, Cardin R, Bortolami M, Guido M, Rugge M. Oxidative damage, pro-inflammatory cytokines, TGF-alpha and c-myc in chronic HCV-related hepatitis and cirrhosis. *World J Gastroenterol* 2006; **12**: 2065-2069

53 **Ogata H**, Chinen T, Yoshida T, Kinjyo I, Takaesu G, Shiraishi H, Iida M, Kobayashi T, Yoshimura A. Loss of SOCS3 in the liver promotes fibrosis by enhancing STAT3-mediated TGF-beta1 production. *Oncogene* 2006; **25**: 2520-2530

54 **Mengshol JA**, Golden-Mason L, Rosen HR. Mechanisms of Disease: HCV-induced liver injury. *Nat Clin Pract Gastroenterol Hepatol* 2007; **4**: 622-634

55 **NIH Consensus Statement on Management of Hepatitis C: 2002.** *NIH Consens State Sci Statements* 2002; **19**: 1-46

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