HEPATITIS C
August 2004

1: Am J Gastroenterol. 2004 Jun;99(6):1099-104.
Amantadine therapy for chronic hepatitis C: a dose escalation study.
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OBJECTIVES: Amantadine reduces liver transaminase levels in some patients with chronic hepatitis C at doses of 200 mg daily and may improve the sustained virological response (SVR) when given with interferon and ribavirin. The primary purpose of the present investigation was to study the safety and toxicity of higher doses of amantadine in subjects who previously failed or were intolerant to interferon. The secondary aim was to test the efficacy of higher dose of amantadine against hepatitis C. METHODS: An open-labeled prospective study was conducted starting with amantadine 200 mg daily and increasing to 500 mg daily while monitoring for safety, toxicity, and efficacy. An amantadine blood level exceeding 1,600 ng/ml was considered toxic requiring dose reduction. The patient's symptoms, laboratory tests, and quality of life were monitored. RESULTS: One hundred patients enrolled in the study. Normalization of alanine aminotransferase (ALT) for each dose was as follows: 200 mg (35%), 300 mg (49%),
400 mg (53%), and 500 mg (56%). The incidence of toxic amantadine plasma levels increased with dose, i.e., 200 mg (0%), 300 mg (6%), 400 mg (27%), and 500 mg (49%). The frequency and severity of arthralgias and fatigue improved at all dosages administered. No changes in the occurrence or severity of headache, insomnia, or depression were reported. Serious adverse events included myocardial infarction and suicide attempt. Other side effects included impotence, confusion, alopecia, and hoarseness. CONCLUSIONS: Amantadine given at
a dose of 300 mg daily is safe, and significantly lowers ALT blood levels more than 200 mg daily. The enzyme response rate does not significantly improve above 300 mg, but toxicity increases.
PMID: 15180732 [PubMed - indexed for MEDLINE]

2: Am J Med. 2004 Jul 1;117(1):10-3.
Comment in:
Am J Med. 2004 Jul 1;117(1):60-1.
Thyroid disorders in chronic hepatitis C.
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PURPOSE: To explore the association of hepatitis C virus (HCV) infection with thyroid disorders. METHODS: We investigated the prevalence of thyroid disorders in 630 consecutive patients with chronic hepatitis due to HCV infection; all patients were free of cirrhosis and hepatocarcinoma, and were not on interferon treatment. Also included were a control group of 389 subjects from an iodine-deficient area, another control group of 268 persons living in an area of iodine sufficiency, and 86 patients >40 years of age with chronic hepatitis B. Levels of thyroid-stimulating hormone (TSH), free thyroxine (T(4)), and triiodothyronine (T(3)), as well as anti-thyroglobulin and anti-thyroid peroxidase antibodies, were measured. RESULTS: Mean TSH levels were higher (P = 0.001), and free T(3) and free T(4) levels were lower (P <0.0001), in patients with chronic hepatitis C than in all other groups. Patients with chronic hepatitis C were more likely to have hypothyroidism (13% [n = 82]), anti-thyroglobulin antibodies (17% [n = 108]), and anti-thyroid peroxidase antibodies (21% [n = 132]) than were any of the other groups. CONCLUSION: Both hypothyroidism and thyroid autoimmunity are more common in patients with chronic hepatitis C-even in the absence of cirrhosis, hepatocellular carcinoma, or interferon treatment-than in normal controls or those with chronic hepatitis B infection.
PMID: 15210382 [PubMed - indexed for MEDLINE]

3: Arch Intern Med. 2004 Jun 28;164(12):1341-6.
A randomized trial of Chinese herbal medicines for the treatment of symptomatic hepatitis C.
Jakkula M, Boucher TA, Beyendorff U, Conn SM, Johnson JE, Nolan CJ, Peine CJ, Albrecht JH.
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BACKGROUND: Many patients with the hepatitis C virus (HCV) cannot be successfully treated with interferon-based regimens. Chinese herbal medicines have been widely prescribed for HCV in Asia, and many infected patients in the United States have used these agents. However, data to support the efficacy of these medications are limited and, to our knowledge, no published trials have been conducted in a US population. METHODS: In a double-blinded design, 45 patients with HCV and fatigue were randomized to receive a combination of Chinese herbal medications or a matched placebo for 12 weeks. The main outcome measures were changes in health-related quality of life using the role physical and vitality scale scores from the validated Hepatitis Quality of Life Questionnaire and alanine aminotransferase levels. In addition, other Hepatitis Quality of Life Questionnaire variables, HCV load, and adverse effects were monitored. RESULTS: In patients with HCV, the herbal medications had no effect on any quality-of-life variables, as measured by the Hepatitis Quality of Life Questionnaire. In addition, no significant changes in alanine aminotransferase or serum HCV RNA levels were noted. No significant adverse effects were observed. CONCLUSIONS: In this study, a regimen of Chinese herbal medicines did not improve quality of life, liver chemistry results, or viral load in a cohort of patients with HCV. Patients and practitioners should remain cautious about the use of herbal medicines for HCV, because studies have not shown a clear benefit of these agents.
Publication Types:
Clinical Trial
Randomized Controlled Trial
PMID: 15226169 [PubMed - indexed for MEDLINE]

4: Arthritis Rheum. 2004 Jul;50(7):2305-8.
Absence of antibodies to cyclic citrullinated peptide in sera of patients with hepatitis C virus infection and cryoglobulinemia.

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OBJECTIVE: To determine if antibodies to cyclic citrullinated peptide (anti-CCP) are found in chronic hepatitis C virus (HCV) infection. METHODS: Rheumatoid factor (RF) and anti-CCP were measured in sera from 50 patients with HCV infection but without cryoglobulinemia, sera from 29 patients with mixed cryoglobulinemia (including 13 with rheumatic symptoms and 5 with arthritis), and sera from 20 normal blood donors. Anti-CCP was measured by second-generation
enzyme-linked immunosorbent assay (ELISA). RESULTS: No sera with elevated anti-CCP were found in patients with HCV infection without cryoglobulinemia, and in that population, the maximum anti-CCP was 10 units, well below the positive cutoff of 20 units. Positive findings on RF testing >13 IU/ml were present in 22 (44%) of the HCV patients, with RF >50 IU/ml in 8 (16%) and a maximum RF of 526 IU/ml. Of the cryoglobulinemia patients, 22 (76%) had positive results on tests for RF, including 18 (62%) with RF >50 IU/ml and a maximum RF of 5,540 IU/ml. Two (6.9%) of the cryoglobulinemia patients had borderline-positive findings on tests for anti-CCP (25 units and 37 units), which were false-positive results caused by nonspecific binding in the ELISA. No association between the RF and the anti-CCP concentrations was found. CONCLUSION: Whereas RF was frequent in patients with HCV infection with and without cryoglobulinemia, anti-CCP was not observed in patients with uncomplicated HCV infection. Borderline-positive anti-CCP results were observed infrequently in patients with mixed cryoglobulinemia and were caused by nonspecific binding to plastic. Measurement of anti-CCP may help in diagnosing RA in patients with chronic HCV infection.
PMID: 15248231 [PubMed - indexed for MEDLINE]

5: Br J Haematol. 2004 Jun;125(6):769-76.
Interest of transjugular liver biopsy in adult patients with haemophilia or other congenital bleeding disorders infected with hepatitis C virus.
Stieltjes N, Ounnoughene N, Sava E, Paugy P, Roussel-Robert V, Rosenberg AR, Terris B, Salmon-Ceron D, Sogni P.
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Liver histology is important for prognosis and treatment strategy in patients with hepatitis C. We report a 10-year experience of transjugular liver biopsy (TJLB) in patients with haemophilia and other congenital bleeding disorders (CBD) in terms of safety, efficiency and therapeutic consequences. TJLB was proposed to patients who were regularly followed for CBD, and were hepatitis C virus (HCV) positive by polymerase chain reaction. Patients with inhibitors or who were human immunodeficiency virus (HIV) positive with CD4 cells <0.2 x 10(9)/l or with evidence of liver failure were excluded. TJLB was performed during a short hospitalization with factor replacement. Between 1992 and 2002, 88 TJLB were performed in 69 of 151 adult HCV patients (39% HIV positive). CBD was haemophilia A in 68% and haemophilia B in 24%. Few mild adverse events were recorded. Histology was assessable in 78 of 88 procedures (89%). Twenty-nine (37%) cases demonstrated minimal change (METAVIR A </= 1 and F </= 1). Extended
fibrosis or cirrhosis was recorded in 23 procedures (26%), all in patients whose infection period was longer than 20 years. No relationship between liver histology, HIV status or HCV genotype was found. TJLB appears to be safe and useful in HCV patients with CBD. One-third of patients had minimal histological changes and could avoid systematic anti-HCV treatment.
PMID: 15180867 [PubMed - indexed for MEDLINE]

6: Curr Drug Targets Infect Disord. 2004 Jun;4(2):163-7.
Novel tissue and cell type-specific gene/drug delivery system using surface engineered hepatitis B virus nano-particles.
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The hepatitis B virus (HBV) surface antigen (HBsAg) L particle is a hollow nano-scale particle. HBsAg L particles have many properties that make them useful for in vivo gene transfer vectors and drug delivery systems. Gene therapy so far has required the in vivo pinpoint delivery of genetic materials into the target organs and cells. Gene transfer by HBsAg L particles might be an attractive method, since their tropism is the same as that of HBV. The HBsAg L particles are able to deliver therapeutic payloads with high specificity to human hepatocytes. In addition, the specificity of L particle can be altered by displaying various cell-binding molecules on the surface. Our results indicate that the L particle is suitable for a cell- and tissue-specific gene/drug transfer vector. In this review, we discuss HBsAg L particles as a gene/drug transfer vector and its potential for the treatment of infectious diseases.
Publication Types:
Review
Review, Tutorial
PMID: 15180463 [PubMed - indexed for MEDLINE]

7: Eur J Immunol. 2004 Jun;34(6):1570-7.
Ultra-sensitive class I tetramer analysis reveals previously undetectable populations of antiviral CD8+ T cells.
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A major breakthrough in cellular immunology has been the development of HLA class I tetramers to analyze CD8(+) T cell responses. However, in many situations, including persistent virus infection, specific T cell responses are rarely detected using this technology. This raises the question of whether such responses are 'deleted' (or 'exhausted') or present below the conventional detection limit for class I tetramer staining. In particular, persistent hepatitis C virus (HCV) infection is characterized by very weak or apparently absent specific CD8(+) T cell responses, even though they are readily detectable in acute disease. Therefore, we assessed the use of anti-PE-labeled magnetic beads to enrich tetramer-positive HCV-specific T cells and identify previously undetectable populations. Using the enrichment technique, HCV-specific T cells could be detected in the majority of infected individuals, whereas these responses were not detected using conventional tetramer staining (8/15 vs. 1/15; p=0.01). Magnetic enrichment could reliably detect very rare HCV-specific responses at frequencies of >0.0011% of CD8(+) T cells (approximately 1/million PBMC), and phenotypic analysis of these rare populations was possible. Therefore, this direct ex vivo technique revealed the persistence of very low frequencies of virus-specific CD8(+) T cells during chronic virus infection and is readily transferable to the study of other viral, self- or tumor-specific T cells.
PMID: 15162426 [PubMed - indexed for MEDLINE]

8: Hepatology. 2004 Jul;40(1):125-32.
Comparison of HCV-specific intrahepatic CD4+ T cells in HIV/HCV versus HCV.
Graham CS, Curry M, He Q, Afdhal N, Nunes D, Fleming C, Horsburgh R, Craven D, Sherman KE, Koziel MJ.
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Persons with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) coinfection are at increased risk for progression to cirrhosis compared with persons with HCV alone, but the reasons for this are unclear. In chronic HCV, the mechanism of liver injury is presumed to be due to HCV-specific T cell destruction of hepatocytes, so it is paradoxical that immunosuppressed hosts have higher rates of fibrosis progression. We examined intrahepatic cellular immune responses to HCV antigens to determine whether there were qualitative or quantitative differences in subjects with and without HIV. Expanded, CD4-enriched, liver-infiltrating lymphocytes from 18 subjects with chronic HCV and 12 subjects with HIV/HCV were cultured in the presence of HCV core protein, nonstructural proteins NS3 and NS5, and recall antigens tetanus toxoid and Candida. Secretion of interferon gamma (IFN-gamma), tumor necrosis factor alpha (TNF-alpha), and interleukin (IL) 10 was determined using enzyme-linked immunosorbent spot assay. There were no significant differences in liver biopsy grade or stage for HIV/HCV versus HCV groups. There were no significant differences between groups in the secretion of IFN-gamma or TNF-alpha in response to HCV or recall antigens. However, there was a significant increase in IL-10 secretion in response to NS3 and NS5 in subjects with HCV compared with HIV and HCV coinfection. In conclusion, subjects with coinfection have an alteration of intrahepatic HCV-specific IL-10 cytokine response that may have implications for HCV-related disease progression.
PMID: 15239095 [PubMed - indexed for MEDLINE]

9: Hepatology. 2004 Jul;40(1):120-4.
A prospective controlled study of interferon-based therapy of chronic hepatitis C in patients on methadone maintenance.
Mauss S, Berger F, Goelz J, Jacob B, Schmutz G.
Center for HIV and Hepatogastroenterology, Dusseldorf, Germany.
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We examined the feasibility of hepatitis C treatment in patients on opioid maintenance. One hundred patients with chronic hepatitis C, 50 on methadone maintenance, and 50 with no intravenous drug use or opioid maintenance for at least 5 years were prospectively matched for sex, age, hepatitis C virus (HCV) genotype and HCV RNA. The primary end point was undetectable HCV RNA at 24 weeks
posttreatment. Treatment with peginterferon alfa-2b (1.5 microg/kg per week) and ribavirin (1000-1200 mg /day) was initiated for 24 weeks (HCV genotype 2, 3) or 48 weeks (HCV genotype 1, 4). Within the first 8 weeks of therapy, discontinuation due to noncompliance or patient request was observed in 22% (11/50) in the methadone group versus 4% (2/50) in the control group (P =.02). After 8 weeks, there was no significant difference in discontinuation due to noncompliance or patient request (4/39 [10%] vs. 4/48 [8%]). There was no difference in discontinuation of therapy because of viral failure or adverse events (10/50 methadone vs. 6/50 control, P =.41). At the end of treatment, 50% (25/50) in the methadone group and 76% (38/50) in the control group had undetectable HCV RNA (P =.01). Sustained viral response was 42% (21/50) in the methadone group and 56% (28/50) in the control group (P =.16). No serious psychiatric event occurred in either group. In conclusion, peginterferon and ribavirin seem reasonably safe and sufficiently effective in patients on methadone maintenance. Patients discontinuing therapy due to noncompliance or request did so early, thereby limiting the cost of an unsuccessful approach to treatment.
Publication Types:
- Clinical Trial
- Controlled Clinical Trial

PMID: 15239094 [PubMed - indexed for MEDLINE]

10: Hepatology. 2004 Jul;40(1):115-9.
Risk of diabetes in HIV infected veterans pre- and post-HAART and the role of HCV coinfection.
Butt AA, Fultz SL, Kwoh CK, Kelley D, Skanderson M, Justice AC.
Division of Infectious Diseases, University of Pittsburgh School of Medicine, and VA Pittsburgh Healthcare System, PA, USA.
We examined the association of hepatitis C virus (HCV) infection with diabetes in veterans infected with human immunodeficiency virus (HIV) before and after the institution of highly active antiretroviral therapy (HAART). The role of age, race, liver disease, alcohol, and drug diagnoses upon the risk of diabetes was also determined. Male veterans with HIV who entered care between 1992 and 2001 were identified from the Veterans Affairs (VA) administrative database. Demographic and disease data were extracted. Kaplan-Meier curves were plotted to determine the incidence of diabetes. Unadjusted and adjusted hazards ratios for diabetes were determined using Cox regression method. A total of 26,988 veterans were studied. In multivariate Cox regression analysis, factors associated with a diagnosis of diabetes included increasing age (HR, 1.44 per 10-year increase in age; 95% CI, 1.39-1.49), minority race (African American: HR, 1.35; 95% CI, 1.24-1.48; Hispanic: HR, 1.63; 95% CI, 1.43-1.86), and care in the HAART era (HR, 2.35; 95% CI, 2.01-2.75). There was a significant interaction between care in the HAART era and HCV infection, with HCV infection being associated with a significant risk of diabetes in the HAART era (HR, 1.39; 95% CI, 1.27-1.53) but not in the pre-HAART era (HR, 1.01; 95% CI, 0.75-1.36). In conclusion, HIV-infected veterans in the HAART era are at a higher risk for diabetes compared with those in the pre-HAART era. HCV coinfection is associated with a significantly higher risk of diabetes in the HAART era, but not in the pre-HAART era. HCV-HIV coinfected patients should be aggressively screened for diabetes.
PMID: 15239093 [PubMed - indexed for MEDLINE]

11: Hepatology. 2004 Jul;40(1):108-14.
Distinct MHC class I and II alleles are associated with hepatitis C viral clearance, originating from a single source.
McKiernan SM, Hagan R, Curry M, McDonald GS, Kelly A, Nolan N, Walsh A, Hegarty J, Lawlor E, Kelleher D.
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The role of cytotoxic T lymphocyte responses, restricted by human leukocyte antigen (HLA) class I alleles, is recognized as highly significant in the successful clearance of hepatitis C virus (HCV). The frequency of class I alleles in females inoculated with HCV genotype 1b from a single source was examined for an association with outcome. Class I typing was performed using polymerase chain reaction sequence-specific primers in 227 female subjects: 141 had chronic infection and 86 had viral clearance. Statistical analysis included chi(2) testing and multiple logistic regression analysis. A*03, B*27, and Cw*01 occurred more frequently in those with viral clearance (39.5%, 14%, and 9.3%, respectively) compared with those with chronic infection (19.1%, 2.1%, and 1.4%, respectively; P < or = .005). B*08 occurred more often in those with chronic infection compared with viral clearance (39.7% vs. 19.8%; P =.002). In combination with previously reported class II allele associations, over 75% that successfully eliminate HCV carry either A*03, DRB1*0101, or *0401, compared with only 37% of those with chronic infection (P <.0001). The haplotypes A*03-B*07-DRB1*15-DQB1*0602 and A*02-B*27-Cw*01-DRB1*0101-DQB1*0501 are
associated with viral clearance (P =.004 and.01, respectively). By multiple

logistic regression analysis, the alleles A*03, B*27, DRB1*0101, *0401, and *15 are associated with viral clearance, and B*27 has the strongest association (odds ratio [OR] 7.99). The haplotype A*01-B*08-Cw*07-DRB1*03011-DQB1*0201 is
associated with chronic infection (P =.002), being independent for DQB1*0201 (OR 0.27). In conclusion, certain class I alleles are associated with outcome in this homogeneous cohort. More significantly, either HLA-A*03, -DRB1*0101, or -*0401 are carried by an overwhelming majority of those subjects who successfully clear HCV.
PMID: 15239092 [PubMed - indexed for MEDLINE]

12: Hepatology. 2004 Jul;40(1):98-107.
Long-term follow-up after successful interferon therapy of acute hepatitis C.
Wiegand J, Jackel E, Cornberg M, Hinrichsen H, Dietrich M, Kroeger J, Fritsch WP, Kubitschke A, Aslan N, Tillmann HL, Manns MP, Wedemeyer H.
Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Germany.
Early treatment of acute hepatitis C infection with interferon alfa-2b (IFN-alpha-2b) prevents chronicity in almost all patients. So far, no data are available on the long-term outcome after interferon (IFN) therapy of acute hepatitis C. The aim of this study was to assess the clinical, virological, and immunological long-term outcome of 31 successfully treated patients with acute hepatitis C infection who were followed for a median of 135 weeks (52-224 weeks) after end of therapy. None of the individuals had clinical evidence of liver disease. Alanine aminotransferase (ALT) levels were normal in all but 1 patient. Serum hepatitis C virus (HCV) RNA was negative throughout follow-up, even when investigated with the highly sensitive transcription-mediated amplification (TMA) assay (cutoff 5-10 IU/mL). In addition, no HCV RNA was detected in peripheral blood mononuclear cells (PBMC) of 15 cases tested. The patients' overall quality-of-life scores as determined by the SF-36 questionnaire did not differ from the German reference control cohort. Ex vivo interferon gamma (IFN-gamma) ELISPOT analysis detected HCV-specific CD4(+) T-helper cell reactivity in only 35% of cases, whereas HCV-specific CD8(+) T-cell responses were found in 4 of 5 HLA-A2-positive individuals. Anti-HCV antibody levels decreased significantly during and after therapy in all individuals. In conclusion, early treatment of symptomatic acute hepatitis C with IFN-alpha-2b leads to a long-term virological, biochemical, and clinical response. Waning of anti-HCV humoral immunity and presence of HCV-specific CD8(+) (but not CD4(+)) T
cells highlights the complexity of T-cell and B-cell memory to HCV, which might be significantly altered by IFN treatment.
PMID: 15239091 [PubMed - indexed for MEDLINE]

13: Hepatology. 2004 Jul;40(1):87-97.
Effects of antiviral therapy on the cellular immune response in acute hepatitis C.
Rahman F, Heller T, Sobao Y, Mizukoshi E, Nascimbeni M, Alter H, Herrine S, Hoofnagle J, Liang TJ, Rehermann B.
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Spontaneous recovery occurs in a minority of patients with acute hepatitis C but is associated with vigorous and long-lasting cellular immune responses. Treatment-induced recovery can be achieved in the majority of patients who are treated in the acute phase, but the kinetics and mechanisms of viral clearance and immune responsiveness are not known. Both direct antiviral effects and indirect immune-mediated effects, such as immune modulation of Th2 to Th1

responses and prevention of exhaustion of cellular responses by rapid reduction of viral titer, have been proposed. To investigate how early antiviral therapy affects hepatitis C virus (HCV)-specific T cell responses, we performed detailed prospective clinical, virological, and immunological studies on 7 patients with acute hepatitis C who received antiviral therapy and were followed at 2 to 4 week intervals for 1 to 2 years. The total CD4(+) and CD8(+) cell response was analyzed with 600 overlapping HCV peptides and 6 proteins by ex vivo enzyme-linked immunospot (ELISpot), intracellular cytokine staining, and proliferation assays. In contrast to earlier studies with selected HCV epitopes, this extended analysis detected multispecific interferon gamma(+) (IFN-gamma(+)) responses in each patient, even in the absence of T-cell proliferation. After initiation of antiviral therapy (at a mean of 20 weeks after infection), all sustained responders demonstrated gradually decreasing, then nearly absent HCV-specific T-cell responses, whereas the sole patient who developed viral breakthrough after initial HCV control maintained cellular immune responses. In conclusion, a sustained response to antiviral therapy was not associated with a lasting enhancement of HCV-specific T-cell responsiveness in the blood.
PMID: 15239090 [PubMed - indexed for MEDLINE]

14: Infection. 2004 Jun;32(3):153-6.
Sequential changes of hepatitis C virus antibody profiles during treatment of chronic hepatitis C of genotype 1b: pretreatment antibody response to E2/NS1 correlated sustained response.
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BACKGROUND: This study aimed to investigate the relation between hepatitis C virus (HCV) antibody profiles and response to therapy of chronic HCV infection of genotype 1b. MATERIALS AND METHODS: Quantitative assays of antibody response
to HCV antigens were performed sequentially using immunoblot confirmatory assays in 25 patients with genotype 1b chronic hepatitis C who received a 24-week course of interferon and ribavirin therapy. RESULTS: 12 patients had a sustained response (group A), and 13 did not (group B). Serum titers of HCV RNA were significantly higher in group B than in group A (p = 0.02). Pretreatment antibody reactivity to core, NS3, NS4, and NS5 antigens did not differ significantly between the two groups, but group A had significantly higher titers of anti-E2/NS1 than group B (p = 0.04). Sustained response was noted in none of seven patients with HCV RNA > 10(6) copies/ml, but did occur in 12 of 18 patients with HCV RNA < 10(6) copies/ml (p < 0.01). Among the latter, all seven patients with anti- E2/NS1 had sustained responses, as did five (45%) of 11 without (p = 0.04). Antibody profiles changed little or not at all at the end of treatment or at 6 months after treatment in both groups. CONCLUSION: In chronic hepatitis C of genotype 1b, patients with HCV RNA > 10(6) copies/ml respond poorly to therapy compared to those with HCV RNA < 10(6) copies/ml. Among the latter, the presence of pretreatment anti-E2/NS1 correlated with sustained response. Quantitative assay of antibody response to HCV antigens at the end of treatment had no additional value to predict a sustained response. Copyright Urban and Vogel
PMID: 15188075 [PubMed - indexed for MEDLINE]

15: Infection. 2004 Jun;32(3):144-8.
Influence of chronic coinfection with hepatitis B and C virus on liver histology.
Sagnelli E, Pasquale G, Coppola N, Scarano F, Marrocco C, Scolastico C, Santantonio T, Gentile A, Piccinino F.

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BACKGROUND: Few data are available on histological features of chronic hepatitis B (HBV) and C (HCV) virus coinfection. PATIENTS AND METHODS: We enrolled 142 consecutive patients with viral chronic hepatitis on their first liver biopsy: 27 HBsAg and anti-HCV positive (case BC group), 57 HBsAg positive and anti-HCV negative (control B group) and 58 anti-HCV positive, HBsAg/anti-HBs/anti-HBc negative (control C group). RESULTS: Patients in the case BC group showed serum HBVDNA (37% vs 71.9%, p < 0.005) and ground-glass hepatocytes (37% vs 66.7%, p < 0.01) less frequently than those in the control B group. The case BC group showed a lower prevalence of patients with detectable HCV-RNA than the control C group (60% vs 92.3%, p < 0.001) and a significantly higher fibrosis score (2.1 +/- 1.2 vs 1.5 +/- 1.1, p < 0.05). Of the 27 patients in the case BC group, 10 lacked serum HCV-RNA and showed significantly higher histological activity index (HAI) and fibrosis scores than those found in the 17 HCV-RNA positive (8.5 +/- 4.4 vs 5.4 +/- 2.4 for HAI, p < 0.05; 3.0 +/- 1.3 vs 1.69 +/- 1.0, p < 0.05 for fibrosis). CONCLUSION: Liver histology seems to be more severe in chronic coinfection with HBV and HCV than in single infection, particularly when HCV replication is impaired. Copyright Urban and Vogel
PMID: 15188073 [PubMed - indexed for MEDLINE]

16: Infection. 2004 Jun;32(3):138-43.
Natural history of acute symptomatic hepatitis type C.
Wawrzynowicz-Syczewska M, Kubicka J, Lewandowski Z, Boron-Kaczmarska A, Radkowski M.
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BACKGROUND: Spontaneous clearance of hepatitis C virus (HCV) after acute hepatitis C, and the course of chronic HCV infection in patients who did not clear the virus, were studied. PATIENTS AND METHODS: Patients with acute C or non-A, non-B hepatitis who were hospitalized between 1988 and 1998 were called for evaluation in 2001. They were tested for anti-HCV, serum HCV-RNA, HCV-RNA in peripheral blood mononuclear cells (PBMC) and liver enzymes. A liver biopsy was performed on chronically infected patients. The course of acute hepatitis C was compared between HCV-RNA-positive and negative subjects to look for factors that might influence spontaneous viral clearance. Factors influencing more progressive liver disease were analyzed in chronic hepatitis C. RESULTS: Out of 159 acute hepatitis C patients, 77 (48.4%) participated in the study, and the median observation time was 8 years. Spontaneous clearance of serum HCV was found in 23 subjects (29.9%), but in two cases HCV-RNA was detected in peripherical blood mononuclear cells (PBMC). Only three patients negative for HCV-RNA in serum and PBMC lost anti-HCV. Severity of acute HCV infection and previous alcohol abuse seemed to influence resolution. In non-alcoholic patients, older age at time of primary infection was a significant predictor of virus clearance. In chronic hepatitis C, more than 75% of patients had minimal or mild activity in biopsy, but 40% had advanced fibrosis. Older age at infection, male gender, alcohol abuse, and higher iron content were connected with advanced fibrosis. CONCLUSION: Studies on HCV infection resolution should include at least PBMC testing for HCV-RNA. A healthy carrier state of HCV can be discussed. A longer observation time increased the likelihood of seroreversion. Fibrosis in chronic hepatitis C probably is not a direct result of inflammatory activity. Copyright Urban and Vogel
PMID: 15188072 [PubMed - indexed for MEDLINE]

17: Infection. 2004 Jun;32(3):134-7.
Prevalence and risk factors of hepatitis C infection after cardiac surgery in childhood before and after blood donor screening.
Vogt M, Muhlbauer F, Braun SL, Lang T, Busch R, Lange R, Frosner G, Hess J.
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BACKGROUND: Since 1974, the risk of acquiring non-A non-B hepatitis by blood transfusion is well known. In 1999, children having had polytransfusions (group 1) after cardiac surgery prior to the establishment of routine blood donor screening could be identified as a risk group for hepatitis C (HCV) infection. PATIENTS AND METHODS: In 1991, Germany began screening blood donors for hepatitis C. To describe the risk after the implementation of blood donor screening, we studied 211 children (group 2) having had open heart surgery after 1991 and compared prevalence for anti-HCV antibodies and known risk factors to group 1. RESULTS: None of the 211 patients with cardiac surgery after 1991 had detectable anti-HCV antibodies, compared to 67 of the 458 patients (14.6%) of group 1 ($p < 0.001$). The mean number of operations in both groups was virtually the same (mean 1.7 +/- 0.9 in group 1, mean 1.6 +/- 0.9 in group 2, $p = 0.075$), whereas the total number of blood products per patient differed significantly (group 1 mean 8 +/- 17.6, group 2 mean 3.5 +/- 2.8; $p < 0.001$). Multivariate analysis of risk factors demonstrates affiliation to group 1, transfusion of fresh blood, warm whole blood, heparinized blood ($p < 0.001$) and plasma ($p = 0.004$) as significant. CONCLUSION: After the implementation of blood donor screening, the risk for HCV infection after cardiac surgery in childhood dropped significantly from 14.6% to < 0.5%. These data show the necessity of HCV screening for patients at risk (operations before 1991) and do not favor a general screening for all patients. Copyright Urban and Vogel
PMID: 15188071 [PubMed - indexed for MEDLINE]

18: Int J Cancer. 2004 Aug 10;111(1):81-5.
Role of hepatitis C virus infection in malignant lymphoma in Spain.
de Sanjose S, Nieters A, Goedert JJ, Domingo-Domenech E, Fernandez de Sevilla A, Bosch R, Herrera P, Domingo A, Petit J, Bosch X, Kallinowski B.
Servei d'Epidemiologia i Registre del Cancer, Institut Catala d'Oncologia, Barcelona, Spain. s.sanjose@ico.scs.es
Hepatitis C virus (HCV) has been implicated in the etiology of malignant lymphomas. We estimated the risk of lymphoma associated with detection of HCV infection. Cases (n = 529) were consecutive patients newly diagnosed with a lymphoid malignancy between 1998 and 2002 in 4 centers in Spain. Lymphomas were diagnosed and classified using the WHO Classification. Controls (n = 600) were hospitalized patients matched to the cases by 5-year age group, gender and study center. Several medical conditions associated with severe immunosuppression precluded the eligibility of controls. Patients underwent a personal interview and blood sampling. HCV positive subjects were considered those with antibody response to third generation ELISA or detection of HCV RNA with Amplicor 2.0. Cases were systematically tested for HIV antibodies. We used the chi(2) test and unconditional logistic regression to estimate the odds ratio (OR) and 95% confidence interval (95% CI) for lymphoma associated with HCV. HCV infection was detected in 40 cases (7.5%) and 23 (3.8%) control subjects. Six of 16 patients with HIV-related lymphomas and 4 of 8 organ-recipient-related lymphomas were HCV positive. The analysis, excluding HIV-infected subjects and organ recipients, led to a prevalence of HCV of 5.9% among cases and 3.8% among controls. The age-, gender- and center-adjusted OR for all lymphomas was 1.58 (95% CI = 0.89-2.79). Among all lymphoma categories, HCV was associated with an increased

risk of low grade B-cell lymphomas not otherwise specified (NOS) (OR = 35.98, 95% CI = 4.70-275.4). A 2-fold excess risk associated to HCV was observed for marginal B-cell lymphomas, diffuse large B-cell lymphoma and lymphoma B NOS but the associations were not statistically significant. HCV infection is associated with an increased risk of a broad spectrum of lymphoid neoplasms among non severely immunocompromised subjects in Spain. Copyright 2004 Wiley-Liss, Inc.
PMID: 15185347 [PubMed - indexed for MEDLINE]

19: Int J Cancer. 2004 Aug 10;111(1):76-80.
Hepatitis C virus infection and non-Hodgkin lymphoma: results of the NCI-SEER multi-center case-control study.
Engels EA, Chatterjee N, Cerhan JR, Davis S, Cozen W, Severson RK, Whitby D, Colt JS, Hartge P.
Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD 20892, USA. engelse@exchange.nih.gov
Several studies have noted elevated hepatitis C virus (HCV) prevalence among patients with non-Hodgkin lymphoma (NHL), suggesting that HCV infection increases NHL risk through chronic immune stimulation. Population-based data from the U.S. are lacking. In a population-based case-control study of NHL in the United States, we identified HCV infection using an enzyme immunoassay, confirmed by recombinant immunoblot assay or HCV RNA detection. The association between HCV and NHL was assessed using logistic regression, adjusting for demographic factors, illicit drug use or medical history. Thirty-two of 813 (3.9%) NHL cases and 14 of 684 (2.1%) controls were HCV-infected [odds ratio (OR) 1.96, 95%CI 1.07-4.03]. For separate NHL subtypes, numbers were limited. Nonetheless, positive associations were noted for follicular (OR 2.46, 95%CI 1.01-5.81), marginal zone (3.99, 0-13.6) and mucosa-associated lymphoid tissue (2.04, 0-7.20) NHLs. For all NHLs combined, the HCV-NHL association changed little after adjustment for sex, age, race and study center (OR 1.89, 95%CI 1.00-4.00). HCV was common in controls who had injected drugs (40%) or used other illicit drugs (6.5%), but adjustment for drug use did not affect the HCV-NHL association (OR 1.87, 95%CI 0.95-4.10). Transfusion history was unrelated to HCV status, and adjustment for this exposure did not attenuate the HCV-NHL association (OR 2.15, 95%CI 1.12-4.76). Excluding 4 subjects with a history of hemodialysis or 3 subjects with organ transplants also did not affect the results. Our study demonstrates an association between HCV infection and NHL in the United States. HCV infection may be a cause of NHL. Copyright 2004 Wiley-Liss, Inc.
Publication Types:
Multicenter Study
PMID: 15185346 [PubMed - indexed for MEDLINE]

20: Int J Cancer. 2004 Aug 10;111(1):1-8.
B-cell non-Hodgkin's lymphoma and hepatitis C virus infection: a systematic review.
Negri E, Little D, Boiocchi M, La Vecchia C, Franceschi S.
Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy. evanegri@marionegri.it
A high prevalence of hepatitis C virus (HCV) infection in patients with B-cell non-Hodgkin's lymphoma (B-NHL) has been reported in some, but not all, studies, and the association showed a strong regional variation. We conducted a systematic review of the prevalence of HCV infection in case series of B-NHL and, when an appropriate control group was available, of the odds ratio of B-NHL associated with HCV infection. A high HCV prevalence in B-NHL was found in southern and eastern Europe, Japan and the southern United States, but not in central and northern Europe, Canada, northern United States, or a few Asian

countries. Possible sources of heterogeneity and bias are discussed. The odds ratio of B-NHL for HCV infection was relatively weak, ranging from 2 to 4 in most studies. Thus, even if the observed association were causal, the percentage of cases of B-NHL attributable to HCV infection would be relatively low (10%) also in countries with a high prevalence of HCV infection in the general population, and extremely low in other countries. This may explain apparent inconsistencies between studies. Potential mechanisms of action are also discussed. Copyright 2004 Wiley-Liss, Inc.
Publication Types:
Review
Review, Academic
PMID: 15185336 [PubMed - indexed for MEDLINE]

21: J Clin Virol. 2004 Aug;30(4):313-9.
Inter-laboratory comparison of qualitative and quantitative detection of hepatitis C (HCV) virus RNA in diagnostic virology: a multicentre study (MS) in Italy.
Mancini C, Pisani G, Azzi A, Luisa Zerbini M, Gentili G, Mario Bisso G; MS participants.
Department of Public Health, University "La Sapienza" of Roma, Piazzale Aldo Moro 5, 00185 Rome, Italy. carlo.mancini@uniroma1.it
BACKGROUND: The importance of the standardisation of nucleic acid amplification technology (NAT) assays for the detection of hepatitis C virus RNA is well known today, as many studies carried out in different European countries attest. The results of a previous study performed in Italy (J. Clin. Virol. 1 (2003) 83) by the Italian Society of Clinical Microbiology (AMCLI) showed that the use of external reference standards and of multicentre collaborative studies significantly improves laboratory performance for the qualitative evaluation of HCV RNA. OBJECTIVES: the AMCLI organised a new study on the standardisation of both the qualitative and the quantitative evaluation of HCV RNA with NAT in order to improve the implementation of the diagnostic methods for HCV RNA detection. STUDY DESIGN: seventeen diagnostic centres of major Italian Hospitals participated in this quality control study. The study consisted of testing three panels, each made up of 10 coded samples including negative and positive samples. Positive samples contained four levels of HCV RNA (genotype 1). RESULTS AND CONCLUSION: Seven out of 510 qualitative results obtained were incorrect (1.4%), two false negative and five false positive. The results gave a sensitivity of 99.5% and a specificity of 95.8%. Regarding quantitative tests, the geometric mean (GM) and standard deviation (S.D.) could be calculated only for the three highest HCV RNA levels. The percentage of results within the range of GM +/- 0.5 log(10) varied from 91% to 100%. Some laboratories had some difficulty in the exact quantification of the lowest (3.00 log IU/ml) as well as of the highest viral levels (6.35 log IU/ml) values, very near to the limits of the dynamic range of the assays. The comparison of the results of this study with that previously carried out one confirms that a regular participation in external quality assessment (EQA) assures the achievement of a high proficiency level in the diagnosis of HCV infection.
Publication Types:
Multicenter Study
PMID: 15163420 [PubMed - indexed for MEDLINE]

22: J Clin Virol. 2004 Aug;30(4):283-90.
Prospects for dendritic cell vaccination in persistent infection with hepatitis C virus.
Gowans EJ, Jones KL, Bharadwaj M, Jackson DC.
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Although hepatitis C virus (HCV) is classified in the Hepacivirus genus in the family Flaviviridae, it is unlike most of the other members of this family due to its propensity to cause persistent infections. This persistent infection eventually results in chronic liver disease, cirrhosis and hepatocellular carcinoma in a proportion of infected individuals. It has been difficult to examine correlates of clearance or persistence because most acute phase HCV infections are subclinical or result in symptoms which are non-specific; consequently, acute infections are not generally recognised and patients often present many years later with persistent infection and accompanying chronic liver disease. Nevertheless, seminal studies, performed during the acute phase, have identified a number of factors which are likely to influence the outcome of infection, although it is possible that the mechanism is multifactorial. One of these factors is impairment of dendritic cell function by a mechanism resulting from expression of an HCV protein(s) in these cells. This may be a major factor in the failure of the immune response to expand after HCV infection, leading to persistence. Nevertheless, it may be possible to overcome this defect by autologous transfusion of HCV antigen-loaded, mature dendritic cells and the purpose of this review is to highlight the need and general approaches for developing dendritic cell-based immunotherapy for HCV infection.
Publication Types:
Review
Review, Tutorial
PMID: 15163415 [PubMed - indexed for MEDLINE]

23: J Med Virol. 2004 Aug;73(4):562-5.
Seroprevalence of markers of viral hepatitis in Yemeni healthcare workers.
Shidrawi R, Ali Al-Huraibi M, Ahmad Al-Haimi M, Dayton R, Murray-Lyon IM.
Academic Department of Gastroenterology, Homerton University Hospital, London, United Kingdom. ray.shidrawi@homerton.nhg.uk
The seroprevalence of viral hepatitis in healthcare workers has important public health implications. To assess the risk factors for the acquisition of viral hepatitis in an unvaccinated cohort from an hyperendemic region, 567 healthcare workers from a large hospital in the capital of the Republic of Yemen were interviewed and tested for serological markers of infection with viral hepatitis. 54/543 (9.9%) tested positive for hepatitis B surface antigen (HBsAg), 174/543 (32.0%) had positive hepatitis B core antibodies (anti-HBc), and 19/546 (3.5%) had hepatitis C antibodies (anti-HCV). Age (OR = 1.04, 95% CI 1.02-1.06), male sex (OR = 2.0, 1.32-3.03), and occupation (healthcare workers not carrying out exposure prone procedures, OR = 1.61, 1.06-2.44) were found to be independent predictors for the likelihood of detecting either HBsAg or anti-HBc by multivariate logistic regression analysis. No independent risk factors for anti-HCV positive status were identified. Our findings support the adoption of universal HBV immunisation programmes and infection control precautions. The absence of known risk factors predicting anti-HCV positive serostatus suggests the main mode of transmission of hepatitis C in this cohort in the Yemen remains undiscovered. Copyright 2004 Wiley-Liss, Inc.
PMID: 15221900 [PubMed - indexed for MEDLINE]

24: J Med Virol. 2004 Aug;73(4):548-53.
Failure to diagnose recent hepatitis C virus infections in London injecting drug users.
Aarons E, Grant P, Soldan K, Luton P, Tang J, Tedder R.
Centre of Virology, University College London, London, United Kingdom.
Hepatitis C virus (HCV) infection results in chronic liver disease in a substantial proportion of those infected. Most new cases of HCV infection in the UK are associated with intravenous drug use. It is important to identify these infections because of the implications for the future health of the individuals

concerned and for the control of further spread of infection. However, as hepatitis C infection is characterised by a relatively long asymptomatic period of seronegative viraemia, a laboratory diagnostic protocol that does not test HCV seronegative samples for the presence of HCV RNA may wrongly designate HCV viraemic seronegative individuals as uninfected. Amongst 424 injecting drug users whose serum was sent to our diagnostic laboratory for "HCV screening" over a 14-month period, the prevalence of HCV seropositivity was 48.4%. We retrospectively identified seven individuals for whom there was evidence of recent acquisition of HCV infection. Three of these infections were identified using our routine diagnostic protocol: testing for the presence of HCV-specific antibody and performing HCV RNA testing only on seropositive and seroindeterminate specimens. However, four cases were only identified by HCV RNA testing of HCV seronegative serum. On the basis of these observations, we estimate the incidence of HCV infection amongst London injecting drug users as being 14.3 per 100 person-years. We advocate that all HCV seronegative blood samples obtained from injecting drug users should be tested for the presence of HCV RNA, and suggest that this could be done efficiently by nucleic acid testing the specimens in small pools. . Copyright 2004 Wiley-Liss, Inc.
PMID: 15221898 [PubMed - indexed for MEDLINE]

25: J Med Virol. 2004 Aug;73(4):529-35.
Hepatitis C virus infection in dialysis and chronic liver patients: Viraemia dependent anti-E2-antibody response.
Hanuka N, Sikuler E, Tovbin D, Neville L, Nussbaum O, Mostoslavsky M, Orgel M, Yaari A, Manor S, Dagan S, Hilzenrat N, Shemer-Avni Y.
Laboratory of Liver Research, Department of Virology, Faculty of Health Sciences, Ben-Gurion University, Beer Sheva, Israel.
Cryptic hepatitis C virus (HCV) infection relates to patients infected chronically with HCV that are seronegative but have HCV-RNA. These patients are not identified by the standard serological tests for HCV, which are based on detection of antibodies to core, NS3 and NS5 antigens. They will, therefore, be wrongly diagnosed as non-infected, and are considered as a potential risk for others. Cryptic HCV infection in dialysis units occurs frequently and, due to medical procedures, is a major factor for contracting the virus when unrecognised. This study was conducted in order to assess the humoral immune responses to E2-antigen in sera of patients infected chronically with HCV. Recombinant E2 protein in enzyme linked immunosorbent assay (ELISA) and Western
blot (WB) were used to test the occurrence of anti-E2 antibodies in the sera of patients from the liver clinic and of dialysis patients. The presence of E2 antibodies was found to be correlated with the presence of HCV-RNA and with viral load. Antibodies to the E2 protein could be detected in as many as 30% of the sera from dialysis patients with cryptic HCV infection (HCV-RNA only). The results suggest that detection of anti-E2 antibodies may enhance significantly HCV serological standard testing; especially among patients on dialysis, and that antibodies to envelope E2 protein appear to depend on and correlate with the presence of HCV particles. Copyright 2004 Wiley-Liss, Inc.
PMID: 15221896 [PubMed - indexed for MEDLINE]

26: JAMA. 2004 Jul 14;292(2):243-50.
HIV Infection, hepatitis C infection, and HAART: hard clinical choices.
Kottilil S, Polis MA, Kovacs JA.
Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md, USA.
Abnormalities in hepatic function have become one of the most common complications occurring among human immunodeficiency virus (HIV)-infected

individuals receiving highly active antiretroviral therapy (HAART), and liver disease has become an increasingly important cause of morbidity and mortality in HIV-infected patients. We present a case of a patient with HIV infection and hepatotoxicity that exemplifies the complications currently observed during the treatment of such patients. Hepatotoxicity can be a result of several factors, including a direct effect of HAART, substance abuse, and coinfection with either hepatitis C virus (HCV) or hepatitis B virus. Imaging studies may be helpful in determining the etiology; however, a liver biopsy is often necessary to be able to more accurately determine the relative contributions of different processes. Although coinfection with HCV and HIV has become a common clinical problem, optimal treatment of such patients remains to be defined and must be individualized to maximize benefit and tolerance.
Publication Types:
Case Reports
Clinical Conference
PMID: 15249574 [PubMed - indexed for MEDLINE]

27: Lancet Infect Dis. 2004 Jul;4(7):437-44.
HIV and hepatitis C virus co-infection.
Rockstroh JK, Spengler U.
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Since the decline in HIV-related morbidity and mortality after introduction of highly active antiretroviral therapy (HAART) in 1996, liver disease caused by chronic infection with hepatitis C virus (HCV) has become an increasingly important cause of morbidity and mortality among HIV-infected patients infected parenterally with HCV in more developed countries. A third of HIV-infected individuals in Europe and the USA have HCV co-infection. HIV accelerates HCV liver disease especially when HIV-associated immunodeficiency progresses. With the introduction of pegylated interferon in combination with ribavirin, greatly improved treatment options for patients with HIV and HCV co-infection have become available and have led to sustained virological response rates of up to 40%. Furthermore, recent cohort analyses have shown that immune reconstitution induced by HAART can improve the course of hepatitis C leading to a decline in liver-related mortality. However, patients with HCV co-infection are at increased risk of hepatotoxicity from HAART. Owing to the high rates of HIV and HCV co-infection worldwide, new improved treatment strategies and guidelines for the management of co-infection remain a major future goal.
Publication Types:
Review
Review, Academic
PMID: 15219554 [PubMed - indexed for MEDLINE]

28: N Engl J Med. 2004 Jul 29;351(5):451-9.
Comment in:
N Engl J Med. 2004 Jul 29;351(5):422-3.
Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons.
Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, Peters MG, Koziel MJ, Bhan AK, Alston B, Colquhoun D, Nevin T, Harb G, van der Horst C; AIDS Clinical Trials Group A5071 Study Team.
Massachusetts General Hospital, Boston, MA 02114, USA. rtchung@partners.org
BACKGROUND: Chronic hepatitis C virus (HCV) infection is a cause of major complications in persons who are also infected with the human immunodeficiency virus (HIV). However, the treatment of HCV infection in such persons has been associated with a high rate of intolerance and a low rate of response. We

conducted a multicenter, randomized trial comparing peginterferon plus ribavirin with interferon plus ribavirin for the treatment of chronic hepatitis C in persons coinfected with HIV. METHODS: A total of 66 subjects were randomly assigned to receive 180 microg of peginterferon alfa-2a weekly for 48 weeks, and 67 subjects were assigned to receive 6 million IU of interferon alfa-2a three times weekly for 12 weeks followed by 3 million IU three times weekly for 36 weeks. Both groups received ribavirin according to a dose-escalation schedule. At week 24, subjects who did not have a virologic response (those who had an HCV RNA level greater than or equal to 60 IU per milliliter) underwent liver biopsy, and medications were continued in subjects with either a virologic response or histologic improvement. RESULTS: Treatment with peginterferon and ribavirin was associated with a significantly higher rate of sustained virologic response (an HCV RNA level of less than 60 IU per milliliter 24 weeks after completion of therapy) than was treatment with interferon and ribavirin (27 percent vs. 12 percent, P=0.03). In the group given peginterferon and ribavirin, only 14 percent of subjects with HCV genotype 1 infection had a sustained virologic response (7 of 51), as compared with 73 percent of subjects with an HCV genotype other than 1 (11 of 15, P<0.001). Histologic responses were observed in 35 percent of subjects with no virologic response who underwent liver biopsy. CONCLUSIONS: In persons infected with HIV, the combination of peginterferon and ribavirin is superior to the combination of interferon and ribavirin in the treatment of chronic hepatitis C. These regimens may provide clinical benefit even in the absence of virologic clearance. The marked discrepancy in the rates of sustained virologic response between HCV genotypes indicates that strategies are needed to improve the outcome in persons infected with HCV genotype 1.
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Publication Types:
Clinical Trial
Multicenter Study
Randomized Controlled Trial
PMID: 15282352 [PubMed - indexed for MEDLINE]

29: N Engl J Med. 2004 Jul 29;351(5):438-50.
Comment in:
N Engl J Med. 2004 Jul 29;351(5):422-3.
Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients.
Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A, Carosi G, Sasadeusz J, Katlama C, Montaner J, Sette H Jr, Passe S, De Pamphilis J, Duff F, Schrenk UM, Dieterich DT; APRICOT Study Group.
Department of Medicine, Division of Infectious Diseases, University of California, San Diego, AntiViral Research Center, CA 92103, USA.
ftorriani@ucsd.edu
BACKGROUND: Hepatitis C virus (HCV) infection is highly prevalent and is associated with substantial morbidity and mortality among persons infected with the human immunodeficiency virus (HIV). We compared the efficacy and safety of pegylated interferon alfa-2a (peginterferon alfa-2a) plus either ribavirin or placebo with those of interferon alfa-2a plus ribavirin for the treatment of chronic HCV infection in patients who were also infected with HIV. METHODS: A total of 868 persons who were infected with both HIV and HCV and who had not previously been treated with interferon or ribavirin were randomly assigned to receive one of three regimens: peginterferon alfa-2a (180 microg per week) plus ribavirin (800 mg per day), peginterferon alfa-2a plus placebo, or interferon alfa-2a (3 million IU three times a week) plus ribavirin. Patients were treated for 48 weeks and followed for an additional 24 weeks. The primary end point was a sustained virologic response (defined as a serum HCV RNA level below 50 IU per

milliliter at the end of follow-up, at week 72). RESULTS: The overall rate of sustained virologic response was significantly higher among the recipients of peginterferon alfa-2a plus ribavirin than among those assigned to interferon alfa-2a plus ribavirin (40 percent vs. 12 percent, P<0.001), or peginterferon alfa-2a plus placebo (40 percent vs. 20 percent, P<0.001). Among patients infected with HCV genotype 1, the rates of sustained virologic response were 29 percent with peginterferon alfa-2a plus ribavirin, 14 percent with peginterferon alfa-2a plus placebo, and 7 percent with interferon alfa-2a plus ribavirin. The corresponding rates among patients infected with HCV genotype 2 or 3 were 62 percent, 36 percent, and 20 percent. Neutropenia and thrombocytopenia were more common among patients treated with regimens that contained peginterferon alfa-2a, and anemia was more common among patients treated with regimens containing ribavirin. CONCLUSIONS: Among patients infected with both HIV and HCV, the combination of peginterferon alfa-2a plus ribavirin was significantly more effective than either interferon alfa-2a plus ribavirin or peginterferon alfa-2a monotherapy. Copyright 2004 Massachusetts Medical Society
Publication Types:
Clinical Trial
Multicenter Study
Randomized Controlled Trial
PMID: 15282351 [PubMed - indexed for MEDLINE]

30: Neurosci Lett. 2004 Jul 22;365(2):87-91.
Association of interferon-alpha-induced depression and improved treatment response in patients with hepatitis C.
Loftis JM, Socherman RE, Howell CD, Whitehead AJ, Hill JA, Dominitz JA, Hauser P.
Portland VA Medical Center, Behavioral Health and Clinical Neurosciences Division, OR, USA.
Thirty-nine patients with hepatitis C viral infection on interferon-alpha (IFN-alpha) therapy were monitored weekly using the Beck Depression Inventory (BDI). Thirteen of thirty-nine patients (33%) developed IFN-alpha-induced major depressive disorder (MDD). During the course of IFN-alpha therapy, patients who became depressed were treated with citalopram, a selective serotonin reuptake inhibitor (SSRI) antidepressant. Results indicated that: (1) IFN-alpha response rates were significantly higher in those patients who developed IFN-alpha-induced MDD than in those who did not (end-of-treatment response (ETR) rates: 61.5% versus 26.9% and sustained viral response (SVR) rates: 38.5% versus 11.5%), (2) male patients with ETR to IFN-alpha therapy were, on average, approximately 33 pounds lighter in body weight than male patients who did not respond, and (3) gender, race, past history of MDD, and past history of substance abuse were not significantly associated with ETR. In conclusion, our findings suggest that IFN-alpha-induced MDD may be a predictor of a positive response to IFN-alpha therapy, or an indication of optimal dosing.
Publication Types:
Clinical Trial
PMID: 15245784 [PubMed - indexed for MEDLINE]

31: Pediatr Infect Dis J. 2004 Jun;23(6):571-4.
Immunogenicity of inactivated hepatitis A vaccine in children with chronic liver disease.
Majda-Stanislawska E, Bednarek M, Kuydowicz J.
Department and Clinic of Infectious Diseases and Hepatology, Medical University of Lodz, Lodz, Poland.
One and 6 months after vaccination with hepatitis A virus vaccine (HAVRIX 720

Junior), immunologic responses (anti-hepatitis A virus >/=20 mIU/ml) in children with chronic hepatitis C infection seroprotection were 92% (23/25) and 75% (9/12) in children with chronic hepatitis B infection 87% (21/24) and 88% (15/17) and in healthy children 91% (20/22) at both times. A booster dose induced seroprotection in all children.
PMID: 15194843 [PubMed - indexed for MEDLINE]

32: Proc Natl Acad Sci U S A. 2004 Jul 6;101(27):10149-54. Epub 2004 Jun 25.
Neutralizing antibody response during acute and chronic hepatitis C virus infection.
Logvinoff C, Major ME, Oldach D, Heyward S, Talal A, Balfe P, Feinstone SM, Alter H, Rice CM, McKeating JA.
Center for the Study of Hepatitis C, The Rockefeller University, 1230 York Avenue, New York, NY 10021, USA.
Little is known about the role of Abs in determining the outcome of hepatitis C virus (HCV) infection. By using infectious retroviral pseudotypes bearing HCV glycoproteins, we measured neutralizing Ab (nAb) responses during acute and chronic HCV infection. In seven acutely infected health care workers, only two developed a nAb response that failed to associate with viral clearance. In contrast, the majority of chronically infected patients had nAbs. To determine the kinetics of strain-specific and crossreactive nAb emergence, we studied patient H, the source of the prototype genotype 1a H77 HCV strain. An early weak nAb response, specific for the autologous virus, was detected at seroconversion. However, neutralization of heterologous viruses was detected only between 33 and 111 weeks of infection. We also examined the development of nAbs in 10 chimpanzees infected with H77 clonal virus. No nAb responses were detected in three animals that cleared virus, whereas strain-specific nAbs were detected in six of the seven chronically infected animals after approximately 50 weeks of infection. The delayed appearance of high titer crossreactive nAbs in chronically infected patients suggests that selective mechanism(s) may operate to prevent the appearance of these Abs during acute infection. The long-term persistence of these nAbs in chronically infected patients may regulate viral replication.
PMID: 15220475 [PubMed - indexed for MEDLINE]

33: Transplantation. 2004 Jun 27;77(12):1834-42.
Factors differentially correlated with the outcome of liver transplantation in hcv+ and HCV- recipients.

Velidedeoglu E, Mange KC, Frank A, Abt P, Desai NM, Markmann JW, Reddy R, Markmann JF.
Department of Surgery, University of Pennsylvania Hospital, 4th Floor Silverstein, 3400 Spruce Street, Philadelphia, PA 19104, USA.
BACKGROUND: Survival following liver transplantation for hepatitis C virus (HCV) is significantly poorer than for liver transplants performed for other causes of chronic liver disease. The factors responsible for the inferior outcome in HCV+ recipients, and whether they differ from factors associated with survival in HCV- recipients, are unknown. METHODS: The UNOS database was analyzed to identify factors associated with outcome in HCV+ and HCV- recipients. Kaplan-Meier graft and patient survival and Cox proportional hazards analysis were conducted on 13,026 liver transplants to identify the variables that were differentially associated with outcome survival in HCV- and HCV+ recipients. RESULTS: Of the 13,026 recipients, 7386 (56.7%) were HCV- and 5640 were HCV+. In
HCV- and HCV+ recipient populations, five-year patient survival rates were 83.5% vs. 74.6% (P<0.00001) and five-year graft survival rates 80.6% vs. 69.9%

(P<0.00001), respectively. In a multivariate regression model, donor age and recipient creatinine were observed to be significant covariates in both groups, while donor race, cold ischemia time (CIT), female to male transplants, and recipient albumin were independent predictors of survival of HCV- recipients. In the HCV+ cohort, recipient race, warm ischemia time (WIT), and diabetes also independently predicted graft survival. CONCLUSIONS: A number of parameters are differentially correlated with outcome in HCV- and HCV+ recipients of orthotopic liver transplantation. These findings may not only have practical implications in the selection and management of liver transplant patients, but also may shed new insight into the biology of HCV infection posttransplant.
PMID: 15223900 [PubMed - indexed for MEDLINE]

34: Virology. 2004 Jul 1;324(2):273-85.
Influence of N-linked glycans on intracellular transport of hepatitis C virus E1 chimeric glycoprotein and its role in pseudotype virus infectivity.
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We have previously reported a functional role associated with hepatitis C virus (HCV) E1 glycoprotein using vesicular stomatitis virus (VSV)/HCV pseudotype. In this study, we have investigated the role of glycosylation upon intracellular transport of chimeric E1-G, and in infectivity of the pseudotyped virus. Interestingly, surface expressed E1-G exhibited sensitivity to Endoglycosidase H (Endo H) treatment, which was similar to full-length E1, suggesting that additional complex oligosaccharides were not added while E1-G was in transit from the endoplasmic reticulum (ER) to the mammalian cell surface. As a next step, each of the four potential N-linked glycosylation sites located at amino acid position 196, 209, 234, or 305 of the E1 ectodomain were mutated separately (asparagine --> glutamine), or in some combination. FACS analysis suggested that mutation(s) of the glycosylation sites affect the translocation of E1-G to the cell surface to different extents, with no single site being particularly essential. VSV pseudotype virus generated from glycosylation mutants exhibited a decrease in titer with an increasing number of mutations at the glycosylation sites on chimeric E1-G. In a separate experiment, N-glycosidase F treatment of pseudotype generated from the already synthesized E1-G or its mutants decreased virus titer by approximately 35%, and the neutralization activity of patient sera was not significantly altered with N-glycosidase F-treated pseudotype virus. Taken together, our results suggested that E1-G does not add complex sugar moieties during transport to the cell surface and retain the glycosylation profile of its parental E1 sequence. Additionally, the removal of glycans from the E1-G reduced, but does not completely impair, virus infectivity.
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Community-based survey of HCV and HIV coinfection in injection drug abusers in Sichuan Province of China.
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AIM: To investigate the prevalence and risk factors of HCV/HIV coinfection in injection drug abusers (IDAs) in Lianshan Yi Autonomous Prefecture of Sichuan province, China. METHODS: From November 8, 2002 to November 29, 2002, a community-based survey was conducted to investigate the demographic characteristics, patterns of shared injectors devices and sexual behaviors in IDAs. Blood samples were also collected to test HCV and HIV infection. A total

of 379 subjects were recruited in the study through community outreach and peer recruiting methods. RESULTS: Of the 379 IDAs, the HCV prevalence and HIV prevalence were 71.0% and 11.3%, respectively, and HCV/HIV coinfection was 11.3%. HCV infection was found in 100% and 67.3% of HIV-positive and HIV-negative IDAs, respectively. HIV prevalence was 16.0% in HCV positive IDAs while none of the HCV negative IDAs was positive for HIV. Ethnicity, shared needles or syringes and cotton in the past 3 mo and syphilis infection were associated with HCV/HIV coinfection shown by univariate analysis using chi-square test. Multivariate logistic regression analysis showed that shared needles or syringes in the past 3 mo (Odds ratio=3.121, 95% CI: 1.278-7.617, P<0.05) and syphilis infection (Odds ratio=2.914, 95% CI: 1.327-6.398, P<0.01) were significantly associated with HCV infection. No statistically significant association was found in univariate analysis between sexual behaviors and HCV/HIV coinfection. CONCLUSION: Shared needles and syringes in the past 3 mo and syphilis infection were significantly associated with HCV infection. Further sero-epidemiological prospective cohort studies should be conducted to clarify the impact of syphilis and high risk sexual behaviors on HCV transmission through unprotected sexual intercourse.
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