Coinfection of Schistosoma species with Hepatitis B or Hepatitis C Viruses

Table 1.3.5 Studies Conducted on Subjects with Hepatitis C Virus

No	Reference	Location (Years)	Study Design (Objective) and Study Population	Exclusion Criteria	Diagnosis of Disease	Findings on Coinfection
1	Kamal et al 2001b	Ain Shams University, Cairo, Egypt (1992-1994)	*Cohort* (comparative, disease progression, severity, immunology): <u>Patient groups:</u> 15 acute HCV and 17 acute HCV w/Sch patients, mean age 28 years, 66% males; Patients were consecutive, symptomatic, and followed for a mean of 72 +/- 4.6 months.	No HBV, HAV, HEV, autoimmune, or alcoholic or drug-related causes	<u>Acute HCV</u>: ALT (20x normal) w/anti-HCV w/HCV RNA; <u>Sch</u>: history, stool/rectal biopsy SchAb, ultrasound;	Viral loads were higher in coinfected at baseline, otherwise comparable to mono HCV patients with respect to age, gender, peak ALT at entry, source of HCV (genotype 4) infection and absence of fibrosis; at follow-up, 33% of mono acute HCV patients had recovered vs. 0% of coinfected; based on paired liver biopsies taken at entry and again after 6 years, coinfected had dramatically higher fibrosis progression rates compared to mono HCV subjects (0.53 vs. 0.1 units per year); coinfected subjects had either absent or transient weak HCV-specific CD4+ T cell responses with Th0/Th2 cytokine production, which at week 12 was inversely correlated with fibrosis progression.

Table 1.3.5 Studies Conducted on Subjects with Hepatitis C Virus

2	El-Refaei et al 2003	Al Azhar University Hospital, Cairo, Egypt (n.a.)	*Case Control* (comparative, immunology): Case groups: 14 chronic HCV and 13 chronic HCV w/Sm patients, ages 18 years and over; Controls: 6 local subjects without evidence of Sm or HCV, matched by age	No HCC, HAV, HBV, HDV, HIV, Epstein-Barr virus, pregnancy, history of alcoholic liver disease or autoimmune hepatitis; none of the subjects had received IFN-alpha therapy.	Chronic HCV: anti-HCV w/ elevated ALT GE 6 months; detectable HCV-RNA; Sch(Sm): patient history w/stool, SchAb;	Coinfected subjects had fewer late differentiated HCV-specific CD8+T cells compared to HCV mono infected subjects, but were comparable with respect to early differentiated cells; Net CD8+T cell responses were comparable between groups as were IL-15 levels; Coinfection appears to target a specific subset of memory CD8+ T cells in HCV infection.
3	El-Refaei et al 2004	Al Azhar University Hospital, Cairo, Egypt (n.a.)	*Case Control* (comparative, immunology, genetics): Case groups: 15 chronic HVC and 23 chronic HCV w/Sm patients, aged 18 years and over; Controls: 10 local individuals, matched by age without evidence of Sm or HCV.	No HCC, HAV, HBV, HDV, HIV, Epstein-Barr virus, pregnancy, history of alcoholic liver disease or autoimmune hepatitis, previous IFN-alpha therapy w/Ribavirin.	Chronic HCV: anti-HCV w/ elevated ALT GE 6 months; detectable HCV-RNA; Sch(Sm): patient history, w/stool, SchAb;	Coinfected subjects had altered cytokine profiles, with lower IFN-gamma and higher IL-10 levels than mono-infected subjects; however, the decrease in IFN-gamma levels observed in the coinfected did not appear to be associated with a decrease in the number of HCV-specific T cells that produced IFN-gamma; Egyptians infected with HCV genotype 4 can mount HCV-specific T cell responses (both CD 4+ and CD8+) despite the prevalence of concomitant Sch.
4	El-Shorbagy et al 2004	Zagazig University, Egypt (2000-2003)	*Cross-sectional* (severity, risk factors): Subjects: 109 HCVRNA+ patients,	No signs or symptoms of advanced liver disease, or other significant medical	Sch: stool, SchAb, ultrasound, liver biopsy; HCV: anti-HCV w/HCV-RNA;	Nearly half of all patients tested positive for SchAb; Coinfected patients had greater hepatic fibrosis than those with mono HCV (OR 7.6, 95% CI 1.9-35.5); coinfection, along with age GE 45

Table 1.3.5 Studies Conducted on Subjects with Hepatitis C Virus

			aged 5-78 years, 71% male	diseases other than those under study		years and a positive history of blood transfusion was associated with severe hepatic pathology, and may warrant special attention with more intensive follow up.
5	ElSammak et al. 2006	Alexandra University, Alexandria, Egypt (n.a.)	*Case Control* (comparative, complications): Case groups: 30 HCV, 30 HCV w/Sch Hepatic Fibrosis, and 30 HCV w/Sch associated HCC patients; Mean ages 44-50 years, 73%-93% male; Controls: 30 healthy subjects, mean age 43 years, 80% male.	No HBsAg+, non-organ specific auto-antibodies, hereditary defects, history of alcohol consumption, use of certain medications including corticosteroids and heparin.	HCV: anti-HCV, HCV RNA; SHF: ultrasound, SchAb, HCC/other LD: ultrasound, elevated AFP, liver biopsy	Coinfected patients displayed higher serum activin A levels compared to those with HCV alone, along with a concomitant reduction in serum IGF-1; Activin A levels were highest among those with HCC and lowest among controls; activin A may represent a potential prognostic tool to determine the severity of liver cirrhosis as it correlated with Child Pugh score and appears to be a predictor for the development of HCC.
6	Emam et al 2006	Zagazig University Hospitals, Zagazig, Egypt (n.a.)	*Case Control* (comparative, immunology, complications): Case groups: 18 chronic HCV and 17 chronic HCV w/Sch patients, mean age 45 years, 57% male; Controls: 15 healthy subjects with no evidence or history of HBV, HCV or Sm, matched for age and sex	No HIV, HBV, liver cirrhosis, HCC or alcoholic liver disease; no patients had IFN-gamma and/or ribavirin treatment within 12 months prior to sample collection.	Chronic HCV: anti-HCV w/HCV-RNA w/elevated ALT for GT 6 months; Sch: patient history, w/SchAb, stool/rectal snip;	While HCV-RNA viral load was comparable between mono and coinfected HCV groups, coinfected subjects had lower IFN-gamma and higher IL-4 and IL-10 levels in comparison with mono-chronic HCV patients or healthy control; It was also noted that IL-4 and IL10 levels did not correlate with one another, or with histological activity index or HCV viral load in any group.

Table 1.3.5 Studies Conducted on Subjects with Hepatitis C Virus

7	Kamal et al 2006	Ain Shams University, Cairo, Egypt (1992-2001)	*Cohort* (comparative, disease progression, severity): Patient groups: 22 acute HCV and 20 acute HCV w/Sm patients, mean age 29 years, 62% male; *Note*: An additional 45 HCV patients, 58% coinfected w/Sm, were used as a validation cohort for the YKL-40 biomarker; Patients were followed for 96 +/- 4.6 months.	Patients had no alcohol consumption, no HIV or HBV; No patient had active Sch.	Acute HCV: anti-HCV for 6 months; Chronic HCV: anti-HCV w/ elevated ALT (10x) and HCV-RNA; Sch(Sm): Ova in stool/rectal biopsy w/ SchAb; SHF: paired liver biopsy; Note: no patient had clinically active Sch	Patients were followed for progression of disease, with paired biopsy at start and end of study; At entry, coinfected had higher HCV RNA titers and TNF-alpha levels than mono infected groups, but otherwise were similar with respect to age, sex, peak ALT, source of infection, HCV genotype and level of liver fibrosis; Within 2 years, coinfected subjects exhibited greater increases in TFG-B levels and YKL-40, suggesting that the fibrotic process was progressing with changes in the extracellular matrix; By the end of the follow-up period, coinfected had more rapid progression to fibrosis than mono HCV subjects (0.61 vs 0.1 units per year) ; Coinfected also developed evidence of Portal hypertension with splenomegaly and esophageal varices, independent of liver fibrosis.
8	Raslan et al 2007	National Research Centre, Cairo, Egypt (n.a.)	*Case Control* (comparative, severity): Case groups: 17 chronic HCV and 13 chronic HCV w/Sch patients, aged 27-67 years, 60% male, 47% liver cirrhosis; Controls: 16 healthy	No extrahepatic failure, metabolic disease, recent systemic infection or active variceal bleeding, recent alcohol intake,	Chronic HCV: anti-HCV w/elevated ALT for GT 6 months; Sch: SchAb; Cirrhosis: ultrasound	Both IGF-1 and IGFBP-3 were lower in subjects with coinfection than in HCV alone and indicative of more severe liver disease; Among the coinfected, mean serum IGFBP-3 were negatively correlated with age and AST levels, and positively correlated with serum albumin and prothrombin; Data suggests that coinfection with Sch may have

Table 1.3.5 Studies Conducted on Subjects with Hepatitis C Virus

			subjects, matched for age and sex	corticosteroid therapy		additional harmful effect on hepatic function beyond that observed on HCV alone.
9	Abbas et al. 2009a	National Liver Institute, Menofeya University, Menofeya, Egypt (2006-2007)	*Cross-sectional* (prevalence, risk factors): Subjects: 119 consecutive patients with chronic HVC related chronic liver disease; 82% male	No B-cell malignancy, immune liver disease, chronic rheumatic disorders or chronic infections from hepatropic agents	Chronic HCV: anti-HCV w/HCV RNA; Sch(Sm): history, abdominal ultrasound w/SchAb, liver biopsy; CG: cryocrit level > 1%	Coinfection with Sch was detected in 62% of the chronic HCV related chronic liver disease patients; The prevalence of Sch coinfection was significantly higher in HCV infected patients without cryoglobulinemia (CG) compared with patients with it; the risk of mixed CG in HCV infected patients might be suppressed by the presence of Sm coinfection and accompanying Th2 response.
10	Abbas et al. 2009b	National Liver Institute, Menofeya University, Menofeya, Egypt (2007-2008)	*Case Control* (comparative, genetics, complications): Case groups: 54 HCV and 55 HCV w/Sch patients, aged 19-67 years, 74% male; Controls: 62 healthy subjects, aged 18 to 56 years, 65% male, without evidence of Sm, HCV or HBV, w/normal LFT; *Note:* all subjects were born in same hyper-endemic rural area where prevalence of	No cirrhosis or other forms of chronic liver disease	HCV: anti-HCV w/HCV-RNA before combination therapy; Sch(Sm): history, stool w/SchAb, rectal biopsy when possible; *Note:* 70% patients treated with PegIFN-alpha and ribavirin for 12 weeks, 30% untreated	Grade of inflammation and stage of fibrous showed no association with IL-10 polymorphisms; Frequency of SM coinfection and IL-10 genotypes/haplotypes were not sig different between non-responders and responders to combination therapy.

Table 1.3.5 Studies Conducted on Subjects with Hepatitis C Virus

			HCV and SM is highest (>15%).			
11	Abdel-Aziz et al 2012	National Liver Institute, Menoufiya University, Menoufiay, Egypt (2010-2012)	*Case Series* (biomarker): Cases: 100 chronic HCV patients, aged 21-60 years, 65% male; Patients were followed before, during and after therapy, and for 6 months later	No cirrhosis, HBV, autoimmune hepatitis	Chronic HCV: anti-HCV w/HCV-RNA for 6 months; Sch: SchAb, Fibrosis: liver biopsy	50% of chronic HCV cases included in this study were SchAb+; There was no difference in the ability to use serum Hyaluronic acid (HA) as marker of liver fibrosis between mono and coinfected HCV groups; HA appears to be a sensitve marker of liver fibrosis, regardless as to the etologic agents involved.
12	Ramadan et al. 2012	Ain Shams University, Cairo, Egypt (n.a.)	*Case Control* (comparative, pathogenesis, inflammatory response): Case groups: 30 chronic HCV and 30 chronic HCV w/Sch patients, mean group aged 46 - 48 years; Controls: 20 healthy subjects, mean age 45 years	No HBsAg+, HIV, liver cirrhosis or renal disease, or other causes of hepatocellular injury such as alcohol and drug related injuries	Chronic HCV: anti-HCV w/HCV RNA w/elevated AAT for GE 6 months; Sch(Sm): Ova in stool, SchAb, liver biopsy	Coinfected patients had higher mean TNF-alpha levels than healthy subjects or subjects with mono HCV; Super oxide dismutase (SOD) levels were lower among all HCV+ subjects, with slightly lower levels among the coinfected; There is a cause and effect relationship between increased levels of TNF-alpha and decreased levels of SOD, relative to the progression of chronic HCV, especially with bilharzial coinfection.

Table 1.3.5 Studies Conducted on Subjects with Hepatitis C Virus

13	Esmat et al 2013	Ain Shams University, Cairo, Egypt (n.a.)	*Cross-sectional* (prevalence, severity, diagnostics): Subjects: 231 chronic HCV patients, aged 18 to 60 years	No other liver diseases, decompensated liver cirrhosis, HCC, liver biopsy contraindication, or unfit for IFN and ribavirin treatment, or BMI >=30 kg/m2; no prior antiviral therapy.	Chronic HCV: anti-HCV w/HCV RNA; Sch: SchAb; Fibrosis: ultrasound, liver biopsy	Coinfection with Sch was detected in 25% of the chronic HCV patients; There was an association between SchAb+ status and the presence of liver fibrosis; as compared with biopsy, the sensitivity of fibroscan was impaired in coinfected patients, particularly in subjects with Portal fibrosis with rare septa or in subjects with numerous septa without cirrhosis.
14	Allam et al. 2014	National Liver Institute, Menoufiya University, Menoufiya, Egypt (n.a.)	*Cross-sectional* (prevalence, severity, virology): Subjects: 141 Health care workers mean age 41 years, 65% male, 70% rural residents *Note*: This is a follow-up of Abdelwahab et al. 2012, reported in Table 1.2.1; No data on the time elapsed between studies is presented.	Patients were unaware of HCV status at time of the initial investigation and had not yet received standard of care at the time this study was undertaken	Spontaneously resolved HCV: anti-HCV wo/HCV-RNA; Current HCV: anti-HCV w/HCV-RNA; Sch(Sm): SchAb, ultrasound; *Note:* Most had HCV genotype 4	48% of the study subjects tested positive for SchAb; A non-sig difference was noted in the frequency of spontaneously resolved HCV cases between the coinfected and mono infected HCV groups (24% vs. 33%) ; Periportal fibrosis found in coinfected subjects (25%), whereas echogenic liver was found in 25% of mono-infected subjects; Overall, coinfected had comparable viral clearance, RNA levels and indicators of liver inflammation to those with mono HCV infection; *Note:* It is unclear what span of time took place between tests conducted on study subjects.

Table 1.3.5 Studies Conducted on Subjects with Hepatitis C Virus

15	Helal et al 1998	Al-Jimi and Tawam Hospitals, United Arab Emirate (1991-1994)	*Cross-sectional* (prevalence, severity): Subjects: 44 patients, aged 20-55 years, 80% male *Note:* All patients were Egyptians, and all patients with Sch were male	No HBsAg+, history of alcohol or drug abuse, autoimmune liver disease; *Note:* Serum samples taken prior to therapy	HCV: anti-HCV; Sch: SchAb, LD: liver biopsy	52% of anti-HCV+ patients were coinfected with Sch; Portal and septal inflammation was present in varying degrees in all subjects; Coinfected subjects had slightly more cirrhosis and mild CAH, while than mono-infected subjects had slightly more moderate CAH; Overall, no sign differences between coinfected and mono infected HCV groups; anti-Sch positivity did not enhance the severity of HCV hepatic pathology; in addition, SchAb+ status did not give a false positive reading for anti-HCV+.
16	Tanaka et al 2005	Kofu in Yamanashi, Katayama in Hiroshima, and Chikugo in Saga/Fukuoka Prefectures, Japan (2001)	*Cross-sectional* (virology): Subjects: 113 HCV-1b patients from endemic Sj areas, mean group ages 67-70, 51% male; Controls: 18 individuals with HCV-1b from non-endemic Sj, mean age 67 years, 50% male.	n.a.	HCV: anti-HCV w/HCV-RNA; Sch (Sj): SchAb w/ultrasound/CT; HCC: patient history, confirmed by ultrasound/CT/liver biopsy	Coinfection with Sj was present in 57% of HCV-1b subjects; HCC occurred more often among the coinfected than HCV alone (45% vs. 23%) ; The molecular evolutionary analysis indicates that the estimated spread of HCV in previously Sj endemic areas in Japan coincides with injection treatment for Sj conducted in 1921.