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Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies

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SUMMARY. A large number of studies have reported on spontaneous viral clearance rates in acute hepatitis C infection, however most have been small, and reported rates have varied quite widely. To improve the precision of the estimated rate of spontaneous viral clearance, a systematic review was conducted of longitudinal studies. Factors associated with viral clearance were also examined. Inclusion criteria for studies were: longitudinal assessment from time of acute hepatitis C; hepatitis C virus RNA analysis as determinant of viral clearance; untreated for acute hepatitis C. Information on study population, and factors that may influence viral clearance were extracted from each study. Viral clearance was defined among individuals with at least 6 months follow-up following acute hepatitis C. The number of subjects with viral clearance was expressed as a proportion for each study and a weighted mean for proportion was calculated. A total of 31 studies were examined. Study populations included nine studies of post-transfusion hepatitis, 19 of acute clinical hepatitis, and three of seroincident cases. In total, data was available for 675 subjects and the mean study population was 22 (range 4–67). The proportion with viral clearance ranged from 0.0 to 0.8, with a weighted mean of 0.26 (95% CI 0.22–0.29). Factors associated with viral clearance were female gender and acute clinical hepatitis C study population. Further studies are required to more clearly define predictors of clearance and guide therapeutic intervention strategies.

Keywords: acute infection, hepatitis C, natural history, observational studies, systematic review, viral clearance.

INTRODUCTION

Soon after the hepatitis C virus (HCV) was identified, a number of cross-sectional studies in people with antibodies to the virus demonstrated that some appeared to have spontaneously cleared the infection, while others maintained a state of viraemia, that was subsequently defined as chronic hepatitis C infection [1–3]. Since then, a number of investigators have endeavoured to characterize the pathogenesis of hepatitis C infection, including the rate, time course and predictors of spontaneous viral clearance [4–11]. Estimates of clearance rates have ranged from 10 to 50% [4–6], and the duration of time to clearance has been found to be as long as 3 years in some cases [7]. Authoritative clinical reviews have generally quoted clearance rates as low as 10–15%.

Abbreviations: ALT, alanine aminotransferase; HCV, hepatitis C virus.

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Factors proposed as being associated with viral clearance in various studies include ethnicity [7,8], icteric clinical presentation [7], absence of HIV infection [8], short incubation period [12], rapid decline in HCV RNA levels [13], specific HLA type II alleles [14,15], and the strength and pattern of HCV-specific CD4 cell responses [16–19].

Interpretability of findings from most studies of viral clearance in acute hepatitis C infection has been limited by the small numbers of reported cases. The largely asymptomatic nature of acute infection has made it difficult to identify cases for investigation, particularly as they are commonly associated with injecting drug use, illegal and stigmatized behaviour, in many countries [20–22]. In order to provide more precise estimates of viral clearance rates, and better define the factors that predict clearance, we undertook a systematic review of acute hepatitis C studies.

METHODS

Search strategy and inclusion criteria

English literature was searched using the MEDLINE database (January 1990 to April 2003) for studies that examined the natural history of acute HCV infection. The search strategies

used were: (hepatitis C OR HCV) AND (acute OR incident OR natural history). The computerized search was supplemented with manual searches of reference lists for additional studies.

Studies were included if they satisfied the following criteria: (i) longitudinal assessment of individual cases from time of acute HCV infection; (ii) at least one follow-up assessment within 24 months of initial diagnosis; (iii) HCV RNA measured and reported for all study subjects; and (iv) individuals untreated for acute HCV infection during follow-up. In studies that included both treated and untreated individuals, only untreated individuals were included in the analyses, provided information was available specific to the untreated group.

We accepted the definition of acute HCV infection used by the authors. Clearance of infection was redefined on the basis of HCV RNA assessment, even if study authors had used other criteria such as elevated serum alanine aminotransferase (ALT) levels. Studies were excluded if they presented either a subgroup or reanalysis of data from another included study. Studies only reported in abstract form were not included.

The following study variables were abstracted for each study: country, method of recruitment, mode of HCV acquisition, number of study subjects, demographic characteristics (age and gender distribution), duration of follow-up, and proportion with clearance of HCV infection. In addition and where available, individual characteristics were abstracted for study subjects.

Statistical analyses

The primary outcome measure was spontaneous clearance of HCV infection (viral clearance) at the time point reported by the authors. The proportion of subjects who cleared was presented for each study with 95% confidence intervals (95% CI). An unweighted mean was determined by calculating the average of the proportions from all studies. The pooled mean of proportions from all included studies was calculated, weighing the overall proportion by sample size. To identify publication bias, heterogeneity was investigated in a funnel plot of proportions of clearance against the study size.

To examine predictors of viral clearance, age at infection was grouped into three categories (≤30, 31–50, >50 years) and genotype into two categories (genotype 1 and nongenotype 1). Subjects that had a 'nondetermined' genotype were excluded from the analysis.

Study population, country of study, and timing of assessment of clearance were also investigated as study predictors associated with viral clearance. Study population was grouped into three categories: post-transfusion, acute clinical hepatitis and sero-incident.

Univariate data comparisons among groups were performed using Stata version 7.0 (StataCorp, College Station, TX, USA). Tests for trend and chi-squared tests were performed for ordinal and nominal categories, respectively, using Epi Info version 6.04 (Centers for Disease Control and Prevention, Atlanta, GA, USA). Regression analyses were performed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA). A $P < 0.05$ was considered significant.

RESULTS

A total of 31 studies of acute hepatitis C with a total of 675 study subjects met the inclusion criteria for this systematic review [7,12,13,16–19,23–46]. Four studies resulted in more than one publication [7,17,19,26,47–50]. In these cases, the most recent or complete was included in the review [7,17,19,26]. Study populations were made up of 19 series of acute clinical hepatitis C, nine of post-transfusion hepatitis C and three of sero-incident cases. The mean study population was 22 (range 4–67) and follow-up ranged from 6 to 157 months (Table 1). All studies enrolled subjects prospectively, although seven of these carried out virological assessments on stored specimens [13,25,28,30,31,33,44].

Criteria for inclusion of acute HCV infection cases varied between the studies. Twenty-one studies included elevated ALT levels within their acute HCV infection definition. Identification of a rise in ALT level ranged between two [27] and 20 [17, 32] times the upper limit of normal. Virtually all (29) studies required seroconversion to anti-HCV antibody and/or HCV RNA for inclusion. The remaining two studies [26, 35] required HCV RNA detection in the presence of elevated ALT levels 10 times the upper limit of normal.

The time at which clearance was measured differed across studies, with seven using 6 months of follow-up [13,17,24,26,28,44,45], a further six studies using 12 months [12,27,30,33,37,42], and the remainder using longer time periods ranging from 18 [29] to 48 months [38,40] after their baseline assessment.

The proportion with viral clearance ranged from 0.0 to 0.8, with an unweighted mean of 0.27 (95% CI 0.20–0.33) and a weighted mean of 0.26 (95% CI 0.22–0.29). Examination of the funnel plot shows symmetry on either side of the weighted mean proportion of viral clearance (Fig. 1). The proportion with viral clearance was not significantly associated with the duration of follow-up ($P = 0.6$).

Viral clearance was less common among males (0.20 *vs* 0.42, RR 0.43, 95% 0.36–0.53) (Table 2). However, viral clearance was not associated with age at infection (*P*-test for trend, $P = 0.36$) and HCV genotype (RR 0.96, 95% CI 0.76–1.21).

Studies based on acute clinical hepatitis C had a higher proportion of viral clearance (0.31, 95% CI 0.26–0.36) than both post-transfusion (0.18, 95% CI 0.13–0.24) and sero-incident studies (0.18, 95% CI 0.09–0.32) ($P = 0.001$) (Table 3).

Taiwan, Japan and Italy were highly represented, with six studies performed in each country. The US had four studies included in the analysis. There was no association between

Table 1 Viral clearance following acute hepatitis C infection: summary of studies

Author (Reference)	Country of study	Population	Risk factors (% of cohort reporting the risk factor)	Gender (M/F)†	Age (years)‡	Follow-up period§ (months)	Number in study	Number of clearers	Proportion (95% CI)
Hofer [13]	Austria	Acute clinical hepatitis	Medical procedure (50%); IDU (25%); sexual (25%)	2/8	38	>6	10	8	0.8 (0.44–0.97)
Chu [26]	Taiwan	Acute clinical hepatitis	Sporadic (100%)	17/7	50	>6	24	8	0.33 (0.16–0.55)
Larghi [35]	Italy	Acute clinical hepatitis	Participation in pharmacokinetics studies (100%)	3/11	30	Mean 45 (range 33–53)	14	8	0.57 (0.29–0.82)
Okayama [37]	Japan	Sero-incident cases	Surgery (50%); anti-HCV-positive spouse (50%)	3/7	57	Mean 149 (range 132–168)	10	2	0.2 (0.03–0.56)
Chu [27]	Taiwan	Post-transfusion hepatitis	Transfusion (100%)	16/6	47	>12	22	4	0.18 (0.05–0.4)
Gursoy [29]	Turkey	Acute clinical hepatitis	Haemodialysis (100%); transfusion (66.6%)	11/7	38	Mean 18	18	1	0.06 (0.001–0.27)
Hjalmarsson [31]	Sweden	Acute clinical hepatitis	Haemodialysis (100%)			Up to 37	5	2	0.4 (0.05–0.85)
Hwang [12]	Taiwan	Post-transfusion hepatitis	Surgery and transfusion (100%)	47/20	52	12	67	14	0.21 (0.12–0.33)
Kamal [32]	Egypt	Acute clinical hepatitis	Occupational exposure (79%); transfusion (6%); dental procedure (6%); IDU (6%); surgery (3%)	21/11	28	Mean 72 ± 4.6	32	5	0.16 (0.05–0.33)
Thimme [16]	US	Acute clinical hepatitis	Needle stick injury (100%)	2/2	40	Range 6–23	4	1	0.25 (0.01–0.81)
Romano [44]	Italy	Acute clinical hepatitis	IDU (64.3%); sexual (14.3%); transfusion (7.1%); unknown (14.3%)	17/12	29	>6	29	4	0.14 (0.04–0.31)
Gerlach [17]	Germany and Italy	Acute clinical hepatitis	Unknown (34.2%); sexual (7.8%); iatrogenic (31.6%); IDU (21.1%); immunoglobulins (5.3%)	16/22	35	Mean 21 (range 6–49)	38	20	0.53 (0.39–0.69)
Lamonaca [34]	Italy	Acute clinical hepatitis	IDU (82%); surgery (4.5%); sexual (9%); needle stick injury (4.5%)	18/4	29	Mean 29 (range 24–48)	22	8	0.36 (0.17–0.59)
Parana [40]	Brazil	Acute clinical hepatitis	Dental procedure (15.4%); household contact (15.4%); tattooing (23.1%); health care profession (15.4%)		32	48	13	2	0.15 (0.02–0.45)
Villano [7]	US	Sero-incident cases	IDU (100%)	28/6	30	Mean 72 (range 14–93)	34	6	0.18 (0.07–0.35)
Amorosa [23]	Italy	Acute clinical hepatitis	IDU (35.7%); transfusion (9.5%); iatrogenic (35.7%); unknown (19.1%)	30/12	29	Range 15–24	42	15	0.36 (0.22–0.52)

Table 1 Viral clearance following acute hepatitis C infection: summary of studies *continued*

Author (Reference)	Country of study	Population	Risk factors (% of cohort reporting the risk factor)	Gender (M/F)†	Age (years)‡	Follow-up period§ (months)	Number in study	Number of clearers	Proportion (95% CI)
Okuda [38]	Japan	Acute clinical hepatitis	Haemodialysis (100%)			Range 36–60	41	4	0.10 (0.03–0.23)
Kobayashi [33]	Japan	Post-transfusion hepatitis	Transfusion (100%)	7/19	43	>36	26	8	0.31 (0.14–0.52)
Prati [42]	Italy	Sero-incident cases	Sexual (20%); iatrogenic (80%)	4/1	39	Median 28 (range 8–36)	5	1	0.2 (0.01–0.72)
Tsai [45]	Taiwan	Acute clinical hepatitis	Transfusion (23.5%); other (76.5%)	8/9	55	Mean 14 (range 8–26)	17	6	0.35 (0.14–0.62)
Chang [25]	Taiwan	Post-transfusion hepatitis	Transfusion (100%)	4/7	50 (median)	12	11	1	0.1 (0.002–0.41)
Missale [18]	Italy	Acute clinical hepatitis	Drug (76%); sexual (15%); needle stick injury (4.5%); surgery (4.5%)	18/3	30	Mean 11 (range 5–23)	21	10	0.48 (0.26–0.70)
Barrera [24]	Spain	Post-transfusion hepatitis	Transfusion (100%)	30/11	56	Mean 72 (range 12–96)	41	5	0.12 (0.04–0.26)
Diepolder [19]	Germany, the Netherlands, Italy	Acute clinical hepatitis	Not defined		37	Mean 18 (range 4–41)	14	8	0.57 (0.29–0.82)
Hino [30]	Japan	Acute clinical hepatitis	Transfusion (75%); sporadic (25%)			12	32	10	0.31 (0.16–0.5)
Naito [36]	Japan	Acute clinical hepatitis	Transfusion (50%); sporadic (50%)	4/2	43	Range 6–14	6	0	0.0 (0.0–0.46*)
Peters [41]	Germany	Post-transfusion hepatitis	Transfusion (100%)			24	13	1	0.08 (0.001–0.36)
Prince [43]	US	Post-transfusion hepatitis	Transfusion (100%)			Mean 29 ± 9	17	3	0.18 (0.04–0.43)
Wang [46]	Taiwan	Post-transfusion hepatitis	Transfusion (100%)	19/10	49	Mean 22 (range 12–43)	29	5	0.17 (0.06–0.36)
Farci [28]	US	Post-transfusion hepatitis	Transfusion (100%)			Mean 157 (range 120–168)	5	1	0.2 (0.01–0.72)
Omata [39]	Japan	Acute clinical hepatitis	Transfusion; sporadic			Mean 31 (range 12–36)	13	2	0.15 (0.02–0.45)
						Mean proportion	Unweighted Weighted (pooled)	0.27 (0.20–0.33) 0.26 (0.22–0.29)	

*One-sided, 97.5% CI.
†Gender available for 22 studies.
‡Mean age at infection (years) available for 23 studies (given as a median in one study).
§Mean follow-up time shown as the mean, median and/or range, dependent on the data provided in each study.

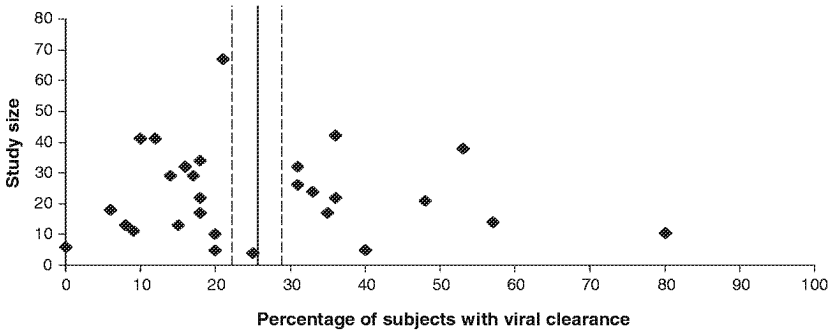

Fig. 1 Funnel plot of the proportion of people with viral clearance against the study size of all studies included in the analysis. The pooled mean (—) and 95% CI (- - -) is shown. Visual examination of the plot reveals symmetry of the individual studies to the overall mean proportion for the 31 studies.

Table 2 Potential predictors of viral clearance

Variable	References	Number of subjects†	Number cleared	Pooled proportion	Relative risk (95% CI)	*P*-value
Age at infection (years of age)	[16,33–37,42,45,46]					
≤30		45	15	0.33		0.36*
31–50		43	18	0.42	0.14 (0.83–1.60)	
>50		55	14	0.26	0.89 (0.69–1.16)	
Total		143	47	0.33		
Gender	[7,12,16,17,32,33,34,35,36,37,42,45,46]					
Female		133	56	0.42	1.0	0.00001
Male		181	36	0.20	0.43 (0.36–0.53)	
Total		314	92	0.29		
HCV genotype	[12,16,17,18,33,34,42,45]					
1		122	41	0.34	1.0	0.76
Other		45	14	0.31	0.96 (0.76–1.21)	
Total		167	55	0.33		

**P*-test for trend.
†Number of subjects who had individual data available for each variable.

Table 3 Study population and country as predictors of viral clearance

Variable	References	Number of subjects	Number cleared	Pooled proportion	Relative risk (95% CI)	*P*-value
Study population						
Post-transfusion	[12,24,25,27,28,33,41,43,46]	231	42	0.18	1.0	0.001
Sero-incident cases	[7,37,42]	49	9	0.18	1.0 (0.56–1.94)	
Acute clinical hepatitis	[16–19,23,26,29–32, 34–36,38–40,44,45]	395	122	0.31	1.70 (1.24–2.32)	
Country of paper publication						
Taiwan	[12,25–27,45,46]	170	38	0.22	1.0	0.08
Japan	[30,33,36,37,38,39]	128	26	0.20	0.91 (0.58–1.41)	
Italy	[18,23,34,35,42,44]	133	46	0.35	1.55 (1.07–2.22)	
US	[7,16,28,43]	60	11	0.18	0.82 (0.44–1.50)	
Other	[17,19,24,29,31,32,40,41]	184	52	0.28	1.26 (0.88–1.82)	

country of study and viral clearance ($P = 0.08$) (Table 3). Other countries represented in this review include Austria, Brazil, Egypt, Germany, Spain, Sweden and Turkey.

DISCUSSION

Examination of the natural history of acute hepatitis C has been limited through small study populations. Our systematic review of 31 longitudinal studies with a total of 675 study subjects indicates that spontaneous viral clearance occurs in approximately one in four people with acute hepatitis C. Studies of acute clinical hepatitis C had higher clearance rates than post-transfusion and sero-incident hepatitis C studies. Female gender was also predictive of viral clearance.

A limitation in estimation of viral clearance in this systematic review is the heterogeneity of studies in terms of sample size, inclusion criteria and follow-up assessments. Mean follow-up was <12 months for many studies, and the majority of studies required both detection of HCV RNA and abnormal ALT level at baseline for case selection. Both these factors could bias the estimate of viral clearance in various ways. As viral clearance often occurs within the first 12 weeks of infection [13], acute hepatitis C cases may have been excluded from studies on the basis of a negative HCV RNA on initial assessment. This may be a particular bias among sero-incident studies, some of which detected with a wide window period. We have recently completed a retrospective cohort study of 99 sero-incident acute HCV infection cases (based on anti-HCV antibody seroconversion within a 2-year window period) among injecting drug users. Analyses from this study estimated viral clearance as ~26% at 2 years within subjects who were HCV RNA positive at anti-HCV antibody seroconversion [9]. However, more than a third of the cohort were HCV RNA negative at seroconversion, and estimates of clearance were higher (~40%) where both HCV RNA-positive and -negative cases at seroconversion were included. This suggests that cases of acute HCV may have been excluded from papers reviewed, based on HCV RNA definition. Consequently, the clearance rate of 26% may be an underestimate. Although viral clearance generally occurs within the initial 6 months of infection, recent studies have suggested that spontaneous clearance extends beyond this point [7,34,35]. Thus, longer-term follow-up in these studies may have also produced higher viral clearance proportions. Although study sample size had a wide range, estimates of viral clearance by weighted and unweighted means were very similar.

Our estimate of 26% spontaneous viral clearance is higher than the 10–15% estimate often provided in reviews of hepatitis C natural history [51]. Given the limitations inherent in studies of acute hepatitis C, particularly the exclusion of initially HCV RNA-negative subjects, the true extent of viral clearance may be even higher. Higher estimates of viral clearance would have important public health implications at both the individual and population levels. The potential for viral clearance needs to be factored into individual counselling. For example, a higher viral clearance rate may act as a disincentive to undertake treatment in early infection. Individual counselling should also cover the risk of HCV reinfection following viral clearance, particularly among individuals at ongoing risk of exposure such as injection drug users. At a population level, estimates and projections of hepatitis C disease burden need to consider the proportion of people with viral clearance. These studies are generally based on population level estimates of HCV antibody prevalence, as opposed to HCV RNA prevalence.

The lack of individual-level demographic and clinical data linked to outcome data in a large proportion of subjects reported in the studies reviewed here made assessment of factors associated to viral clearance difficult. Despite this limitation, viral clearance was associated with gender, with around 40% of female subjects undergoing clearance compared with 19% of male subjects. In contrast, there was no association between viral clearance and age at infection or HCV genotype. The mechanism for the association between spontaneous viral clearance and female gender is uncertain. Various studies have reported high clearance rates in women [10,52–54]. The relationship between female gender and better response rates to interferon therapy has also been demonstrated [55]. It has been hypothesized that HCV clearance in women may be facilitated by oestrogen hormone [52,55]. The higher proportion of subjects with viral clearance in the acute clinical hepatitis C studies is consistent with an association between more symptomatic acute hepatitis C and viral clearance which may be the result of a vigorous broad-based immune response during early HCV infection [13–16].

Although providing important information on the natural history of acute HCV infection, our systematic review highlights the need for larger prospective studies with longer-term follow-up. Ideally, these studies should recruit both acute clinical and sero-incident cases, be representative in terms of demographics and modes of HCV acquisition, and examine behavioural, virological and immunological determinants of both viral clearance and HCV reinfection. Particular emphasis is required to recruit young injecting drug users with acute hepatitis C, as they make up the majority of cases in industrialized country settings.

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