Criteria Grid
Best Practices and Interventions for the Diagnosis and Treatment of Hepatitis C

Best Practice/Intervention:	Franchini M. et al. (2008) Treatment of chronic hepatitis C in haemophilic patients with interferon and ribavirin: a meta-analysis. *Journal of Antimicrobial Chemotherapy*, 61(6):1191-1200.
Date of Review:	February 13, 2015
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☒
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☐ **Other:** _____ **Level:** **Group** ☒ **Individual** ☐ **Other:** _____ **Target Population:** **Haemophilic patients with chronic hepatitis C** **Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin:** **Italy** **Language:** **English** ☒ **French** ☐ **Other:** _____

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☒	☐	☐	meta-analysis; systematic review to analyze the effect of combination therapy (IFN/Peg-IFN and ribavirin) in HCV haemophilic patients
The best practice/intervention has utilized an evidence-based approach to assess:				
Efficacy	☒	☐	☐	Outcome: sustained virological response defined as undetectable HCV-RNA 6 months after the end of treatment
Effectiveness	☐	☒	☐	
The best practice/intervention has been evaluated in more than one patient setting to assess:				

Efficacy	☒	☐	☐	18 studies included for analysis with 824 patients
Effectiveness	☐	☒	☐	

	YES	NO	N/A	COMMENTS
The best practice/intervention has been operationalized at a multi-country level:	☒	☐	☐	Electronic search on MEDLINE, EMBASE, SCOPUS and Cochrane Library
There is evidence of capacity building to engage individuals to accept treatment/diagnosis	☐	☐	☒	
There is evidence of outreach models and case studies to improve access and availability	☐	☐	☒	
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☒	☐	☐	Clear methodology
Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	
Are the best practices/methodology/results described applicable in developing countries?	☒	☐	☐	
Evidence of manpower requirements is indicated in the best practice/intervention	☐	☒	☐	
Juried journal reports of this treatment, intervention, or diagnostic test have occurred	☒	☐	☐	*Journal of Antimicrobial Chemotherapy*
International guideline or protocol has been established	☐	☒	☐	
The best practice/intervention is easily accessed/available electronically	☒	☐	☐	Free for download from http://jac.oxfordjournals.org/
Is there evidence of a cost effective analysis? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	
How is the best practice/intervention funded? ***Please got to Comments section***	☐	☒	☐	No specific funding received

Other relevant information: _____	☐	☐	☐	- HCV in haemophiliacs has similar behavior to that in non-haemophilic patients both in terms of response to IFN-ribavirin therapy and in terms of negative predictors of IFN therapy efficacy

JAC antiviral

Journal of Antimicrobial Chemotherapy (2008) **61**, 1191–1200
doi:10.1093/jac/dkn119
Advance Access publication 19 March 2008

Treatment of chronic hepatitis C in haemophilic patients with interferon and ribavirin: a meta-analysis

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Received 13 December 2007; returned 1 February 2008; revised 20 February 2008; accepted 23 February 2008

***Background*: Hepatitis C virus (HCV) infection is a major cause of morbidity and mortality among haemophilic patients who were treated with clotting factor concentrates before the availability of virus-inactivated factors in the mid 1980s. In order to analyse the effect of the current combination anti-HCV treatment [i.e. ribavirin plus interferon (IFN)] in this subset of HCV-infected patients, we performed a systematic review with meta-analysis of the available literature.**

***Methods*: The outcome was sustained viral suppression. When trials included for the main predictors two arms (positive and negative), the effect size was described as a comparative index [odds ratio (OR)] and a standard meta-analytical procedure was applied. However, when trials did not report the outcome in separate study arms, the effect size was a non-comparative index (success rate) and comparisons between predictor-positive and -negative studies were performed by meta-regression.**

***Results*: Data involving 824 haemophilic HCV-infected patients treated with IFN plus ribavirin were collected from 18 articles (14 prospective cohort studies, 1 retrospective study and 3 randomized controlled trials). The higher rate of sustained viral response was observed in human immunodeficiency virus (HIV)-negative naive haemophiliacs treated with pegylated-IFN in combination with ribavirin (61%, ranging from 45% for genotype 1 to 79% for non-1 genotypes). Genotype 1 (OR, 0.15; 95% CI, 0.09–0.25) and co-infection with HIV (OR, 0.25; 95% CI, 0.08–0.81) were strong predictors of worse response to IFN therapy.**

***Conclusions*: Our meta-analysis shows that the pattern of response to combination anti-HCV therapy of chronically HCV-infected haemophiliacs is similar to that achieved in the general HCV-infected population.**

Keywords: HCV, haemophilia, response

Introduction

Hepatitis C virus (HCV) infection is a major cause of morbidity and mortality in haemophilic patients.[1] In fact, virtually all haemophiliacs who were infused with clotting factor concentrates before the introduction of viral inactivation techniques in the mid 1980s were infected with HCV.[2] Of all infected patients, ~10% to 20% spontaneously clear the virus, as documented by the persistence of serum anti-HCV antibodies with negative serum HCV-RNA, whereas the majority (~80%) develop a chronic hepatic infection which in ~20% of cases progresses to the end stages (cirrhosis, liver failure and hepatocellular carcinoma) after 20 years of infection.[3,4] HCV genotype 1, duration of HCV infection and co-infection with human immunodeficiency virus (HIV) have been identified as important predictors of disease progression.[5–7]

Thus, the antiviral treatment is applied in such patients in order to eradicate HCV and to prevent the development of

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severe liver disease.[8,9] Results in HCV-infected non-haemophilic population have shown that the addition of ribavirin to interferon (IFN) monotherapy has improved the sustained viral response (SVR) from 10–20% to 30–40%.[10–12] When IFN was substituted by pegylated formulation (Peg-IFN), the response to combination therapy increased to 50–60%.[13–15] This association has also rescued a significant proportion of patients refractory (8% to 21% of SVR) or relapsed (42–55 of SVR) to a previous course with IFN alone or in combination with ribavirin.[16,17]

Although treatment response rates seem to be similar in HCV-chronically infected haemophiliacs, the studies published so far are limited and often include a small number of patients.[7,18]

This systematic review is aimed to analyse the existing literature on the combination therapy (IFN or Peg-IFN and ribavirin) in the treatment of chronic hepatitis C in haemophilic patients and to evaluate the influence of factors predictive of the efficacy of therapy on sustained treatment response.

Materials and methods

Literature search

We first performed an electronic search on chronic anti-HCV therapy in haemophiliacs on MEDLINE, EMBASE, SCOPUS and the Cochrane Library without temporal limits using different combinations of the following keywords: 'haemophilia', 'haemophilic patients', 'congenital bleeding disorders', 'hereditary coagulation disorders', 'haemorrhage', 'coagulopathy', 'hepatitis C virus', 'HCV', 'chronic hepatitis C', 'interferon', 'IFN', 'pegylated interferon', 'Peg-IFN', 'ribavirin', 'antiviral therapy' and 'treatment'. In addition, the bibliographic references of all retrieved studies and reviews were assessed for additional reports of clinical trials. Unpublished works were identified by searching the abstract books of the most important conferences on infectious and haematological diseases.

Selection criteria, data collection, outcome and predictors

We included controlled and uncontrolled trials, and randomized or non-randomized studies in the analysis. For inclusion, studies had to enrol patients with a diagnosis of hereditary bleeding disorders and chronic hepatitis with detectable HCV viraemia treated with IFN plus ribavirin or Peg-IFN plus ribavirin. Combination therapies in the studies had to be planned for $\geq$6 months.

The outcome evaluated was the SVR, defined as undetectable HCV-RNA 6 months after the end of treatment. We also recorded, when available, data related to variables that have been proposed as predictors of response to treatment, such as data on HCV genotype, HIV infection status, previous IFN treatment, age at treatment, age at infection and duration of HCV infection.

Quality assessment

The quality assessment varied according to the design of the study. The methodological quality of cohort studies was assessed using an application of the Newcastle–Ottawa quality assessment scale for cohort studies.[19] The scale is aimed to assess for selection bias, comparability of cohorts on the basis of the design or analysis and outcome assessment. The quality of randomized trial was assessed with a scale developed by Jadad *et al*.[20] This scale evaluates the randomization and double-blinding processes, and reports of drop-outs and withdrawals; trial scores range from 0 to 5 points. The randomization process was evaluated in terms of adequacy of sequence generation and allocation concealment. Each trial was independently scored by two of us and any areas of disagreement arbitrated by a third.

Statistical analysis

In all studies selected for inclusion in the meta-analysis, the outcome was the sustained viral suppression, defined as the absence of HCV-RNA at the end of treatment and at the follow-up (24 weeks after the end of treatment). When trials included for the main predictors (e.g. HCV genotype 1, HIV co-infection and Peg-IFN use) two arms (positive and negative), the effect size was described as a comparative index [odds ratio (OR)] and a standard meta-analytical procedure was applied. However, when trials did not report the outcome in separate study arms, the effect size was a non-comparative, descriptive index (success rate) and comparisons between predictor-positive and -negative studies were performed by meta-regression. This index was calculated after logarithmic odds (logit) transformation of proportions, which allows better behaved (e.g. more normally distributed) quantities to be obtained. Weighting of the study results was obtained through the inverse variance method.

A meta-regression was performed in order to estimate the influence of predictors on the outcome (success rate in HCV eradication). The predictors used were presence of HIV-1 co-infection (yes or no), use of Peg-IFN (yes or no) and presence of HCV genotype 1 (yes or no).

Assessment of publication bias and heterogeneity

Clinical heterogeneity was explored and statistical heterogeneity assessed by using the Cochran's Q and estimated using the I^2 statistic and τ^2, which examines the percentage of total variation across studies due to heterogeneity rather than to chance.[21] In order to address the heterogeneity issue and to calculate τ^2, the DerSimonian–Laird method for study weighting and confidence interval (CI) establishing was used. Finally, logits were re-converted into rates and as such reported and graphically plotted.

To inspect for publication bias visually, we generated graphical funnel plots according to Egger *et al*.[22] The statistical methods used for detecting publication bias were the rank correlation tests of Begg and Mazumdar.[23]

Data analysis was completed using STATA 9.2.

Results

In total, we identified 163 references through the electronic and hand searches. After reading the full text of the articles, we excluded 131 irrelevant references (116 focusing on other topics and 15 editorial/reviews) and retrieved 32 potentially relevant references for further assessment. A further 14 studies were excluded because of duplicates of already included studies (7 references) or because the relevant data could not be extracted (7 references). Thus, we have considered 18 studies for this systematic review, with information on 824 patients.[24–41]

Qualitative review

Tables 1 and 2 report the studies in detail with design, patient and treatment characteristics. The majority of the studies utilized

Table 1. Summary of the literature data: characteristics of the patients

Author[ref.]	Study design	Patients' characteristics				
		total	HIV−/naive	HIV−/NR	HIV+/naive	HIV+/NR
Shields *et al.*[24]	open-label, PCS	28	22/28 (78.6)	3/28 (10.7)	3/28 (10.7)	0/28
Sauleda *et al.*[25]	open-label, PCS	20	20/20 (100)	0/20	0/20	0/20
Sauleda *et al.*[26]	open-label, PCS	20	0/20	0/20	20/20 (100)	0/20
Lethagen *et al.*[27]	open-label, PCS	39	39/39 (100)	0/39	0/39	0/39
Schulman *et al.*[28]	open, RCT	61	49/61 (80.3)	12/61 (19.7)	0/61	0/61
Fried *et al.*[29]	open, RCT	113	113/113 (100)	0/113	0/113	0/113
Santagostino *et al.*[30]	open-label, PCS	39	0/39	39/39 (100)	0/39	0/39
Franchini *et al.*[31]	open-label, PCS	33	0/33	33/33 (100)	0/33	0/33
Santagostino *et al.*[32]	open-label, PCS	34	34/34 (100)	0/34	0/34	0/34
Puetz *et al.*[33]	open-label, PCS	11	9/11 (81.8)	2/11 (18.2)	0/11	0/11
Meijer *et al.*[34]	randomized, DB, PC	66	66/66 (100)	0/66	0/66	0/66
Theodossiades *et al.*[35]	open-label, PCS	18	8/18 (44.4)	0/18	10/18 (55.6)	0/18
Husa *et al.*[36]	retrospective study	24	10/24 (41.7)	14/24 (58.3)	0/24	0/24
Au *et al.*[37]	open-label, PCS	17	17/17 (100)	0/17	0/17	0/17
Mancuso *et al.*[38]	open-label, PCS	64	64/64 (100)	0/64	0/64	0/64
Shire *et al.*[39]	open-label, PCS	22	11/22 (50.0)	0/22	11/22 (50.0)	0/22
Posthouwer *et al.*[40]	open-label, PCS	56	40/56 (71.4)	6/56 (10.7)	9/56 (16.1)	1/56 (1.9)
Posthouwer *et al.*[41]	open-label, PCS	159	134/159 (84.3)	0/159	25/159 (15.7)	0/159

NR, non-responders; PCS, prospective cohort study; RCT, randomized clinical trial; DB, double-blind; PC, placebo-controlled.
Results are expressed as number of cases (percentage).

a non-controlled and non-randomized design. There were 14 prospective cohort studies, 1 retrospective study and 3 randomized controlled trials. Twelve studies were performed in HIV-negative patients, 5 studies included both HIV-negative and -positive patients and 1 study included HIV-positive patients only. Of the 824 patients evaluated, 110 (13.3%) were non-responders to previous antiviral therapy, whereas 714 (86.7%) were untreated.

According to the Newcastle–Ottawa quality assessment scale [Table S1, available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/)], the criteria for selection of patients and comparability of cohorts as well as the outcome evaluation were, with few exceptions, satisfactory and homogeneous.

The sequence generation of the randomization process was adequate in all of the three randomized clinical trials; allocation concealment was adequate in one study and unclear in two. One study was described merely as double blind, but no details about blinding were provided. Information regarding withdrawals was described in two studies. The Jadad score of individual studies was 3.

Quantitative analysis

Rates of sustained response to IFN treatment are shown in Tables 2 and 3 and in Figures 1–4. Twelve studies reported the outcome in patients with HCV infection sustained by genotype 1 and in patients with HCV infection sustained by other genotypes (Figure 1), and five studies reported the outcome separately in HIV-infected and non-infected patients (Figure 2). The availability of outcome data in separate arms allowed to calculate conventional pooled estimates and, for this purpose, we used OR and 95% CI. As expected, genotype 1 was associated with lower probability of response compared with other genotypes (OR, 0.15; 95% CI, 0.09–0.25). Moreover, the response to antiviral therapy in HCV–HIV-co-infected patients was lower than in patients without HIV co-infection (OR, 0.25; 95% CI, 0.08–0.81). For other predictive variables (previous IFN treatment, use of Peg- or non-Peg-IFN), since the trials included in the analysis did not report the outcome in separate study arms, or the number of patients analysed in separate arms was too small and the heterogeneity too high to allow a meaningful comparison, we calculated the average proportion of patients with SVR across individual studies, as shown in Table 3. The higher rate of SVR (61%) was reached in HIV-negative naive haemophiliacs treated with Peg-IFN (Figure 3). Moreover, this rate increased up to 79% if the genotype was different from 1. In contrast, the lower SVR rate was observed in HIV-positive naive haemophiliacs treated with Peg-IFN (29%, Figure 4).

Rates of response from randomized trials are limited to three studies conducted in HIV-negative patients (Table 1). In one of these studies, patients were randomized to receive non-Peg-IFN with or without ribavirin; for the purpose of this analysis, we extracted data limited to the combination arm.[29] The other two studies conducted in patients receiving non-Peg-IFN in combination with ribavirin were randomized to a different induction therapy schedule or to a different duration of IFN treatment: in both cases, we extracted data from all patients receiving combination treatment.[28,34] Rate of SVR was 28.5% in the study by Fried *et al.*[29] The studies by Schulman *et al.*[28] and by Meijer *et al.*[34] reported rates of SVR separately for genotype 1 and non-1 genotypes: these figures were 21.9% and 80.0%, and 39.2% and 86.6%, respectively. Overall, rates of responses from randomized trials were within the range of values observed in the cumulative analysis.

Table 2. Summary of the literature data: characteristics of treatment and response

	Treatment characteristics				Sustained viral response				
Author[ref.]	protocol	IFN doses	RBV doses (mg/day)	duration	pooled	HIV−/naive	HIV−/NR	HIV+/naive	HIV+/NR
Shields *et al.*[24]	IFN + RBV	3 MU TW	1000–2000	48 w	20/28 (71.4)	19/22 (86.4)	0/3	1/3 (33.3)	—
Sauleda *et al.*[25]	IFN + RBV	3 MU TW	800–1200	1 y	7/20 (35.0)	7/20 (35.0)	—	—	—
Sauleda *et al.*[26]	IFN + RBV	3 MU TW	800	1 y	8/20 (40.0)	—	—	8/20 (40.0)	—
Lethagen *et al.*[27]	IFN + RBV	3 MU TW	1000–1200	6 m	14/39 (35.9)	14/39 (35.9)	—	—	—
Schulman *et al.*[28]	IFN + RBV	3 MU TW	1000–1200	6 versus 12 m	25/61 (41.0)	22/49 (44.9)	3/12 (25.0)	—	—
Fried *et al.*[29]	IFN + RBV versus IFN	3 MU TW	1000	48 w	16/56 (28.6)	16/56 (28.6)	—	—	—
Santagostino *et al.*[30]	IFN + RBV	5 MU (6 m) + 3 MU (6 m) TW	1000–1200	1 y	14/39 (35.9)	—	14/39 (35.9)	—	—
Franchini *et al.*[31]	IFN + RBV	5 MU TW	1000–1200	1 y	11/33 (33.3)	—	11/33 (33.3)	—	—
Santagostino *et al.*[32]	IFN + RBV	5 MU (6 m) + 3 MU (6 m) TW	1000–1200	1 y	14/34 (41.2)	14/34 (41.2)	—	—	—
Puetz *et al.*[33]	IFN + RBV	3 MU TW	1000	1 y	3/11 (27.3)	2/9 (22.2)	1/2 (50.0)	—	—
Meijer *et al.*[34]	IFN + RBV	5 MU TD (4 w) + 6 MU AD (48 w) versus 5 MU AD (4W) + 6 MU AD (48 w)	1000	52 w	33/66 (50.0)	33/66 (50.0)	—	—	—
Theodossiades *et al.*[35]	Peg-IFN + RBV	Peg-IFN 1.5 μg/kg/w	13 mg/kg/d	48 w	5/18 (27.8)	5/8 (62.5)	—	0/10	—
Husa *et al.*[36]	IFN + RBV Peg-IFN + RBV	IFN 3 MU TW or Peg-IFN 180 μg/w	1000–1200	48 w	8/21 (38.1) 2/3 (66.7)	4/10 (40.0) —	4/11 (36.4) 2/3 (66.7)	— —	— —
Au *et al.*[37]	IFN + RBV	5 MU TW	1000	1 y	7/17 (41.2)	7/17 (41.2)	—	—	—
Mancuso *et al.*[38]	Peg-IFN + RBV	Peg-IFN 1.5 μg/kg/w	800–1200	24 or 48 w[a]	40/64 (62.5)	40/64 (62.5)	—	—	—
Shire *et al.*[39]	Peg-IFN + RBV	Peg-IFN 180 μg/w	800	48 w	8/22 (36.4)	5/11 (45.5)	—	3/11 (27.3)	—
Posthouwer *et al.*[40]	Peg-IFN + RBV	Peg-IFN 1.5 μg/kg/w	800–1200	24 or 48 w[a]	31/56 (55.4)	28/40 (70.0)	1/6 (16.7)	2/9 (22.2)	0/1
Posthouwer *et al.*[41]	IFN + RBV Peg-IFN + RBV	NI	NI	6 m	33/74 (44.6) 50/85 (58.8)	32/72 (44.4) 39/62 (62.9)	—	1/2 (50.0) 11/23 (47.8)	—

NR, non-responders; IFN, interferon; Peg-IFN, pegylated interferon; RBV, ribavirin; MU, millions of units; TW, three times weekly; TD, twice daily; y, years; m, months; w, weeks; AD, alternate days; NI, not indicated.
Results are expressed as number of cases (percentage).
[a]According to genotype.

Table 3. Rates of sustained viral response in subgroups of patients stratified according to predictors; a non-comparative index was calculated after logarithmic odds (logit) transformation of proportions

Subgroup of patients	Rate of sustained viral response (lower and upper limits)	Heterogeneity assessment			
		Q (dof)	P value	I^2 (%)	τ^2
HIV-negative, IFN naive	0.48 (0.41–0.56)	43.38 (15)	<0.001	65.4	0.235
treated with non-Peg-IFN	0.43 (0.34–0.51)	20.6 (9)	<0.001	56.3	0.1569
treated with Peg-IFN	0.61 (0.54–0.68)	5.24 (5)	0.387	4.6	0.0069
HIV-positive, IFN naive	0.36 (0.26–0.48)	5.99 (6)	0.424	0.0	0
treated with non-Peg-IFN	0.40 (0.23–0.60)	0.14 (2)	0.934	0.0	0
treated with Peg-IFN	0.29 (0.13–0.51)	5.66 (3)	0.129	47.0	0.4468
Non-1 genotype (overall)	0.79 (0.71–0.85)	12.41 (11)	0.333	11.4	0.0635
Non-1 genotype (HIV-negative, IFN naive)					
treated with non-Peg-IFN	0.77 (0.66–0.85)	3.21 (6)	0.782	0.0	0
treated with Peg-IFN	0.79 (0.45–0.94)	7.05 (2)	0.029	71.6	1.2585
Genotype 1 (overall)	0.34 (0.25–0.43)	25.39 (11)	0.008	56.7	0.2576
Genotype 1 (HIV-negative, IFN naive)					
treated with non-Peg-IFN	0.34 (0.23–0.46)	17.7 (6)	0.007	66.1	0.3383
treated with Peg-IFN	0.45 (0.33–0.57)	1.4 (2)	0.496	0.0	0

dof, degrees of freedom.

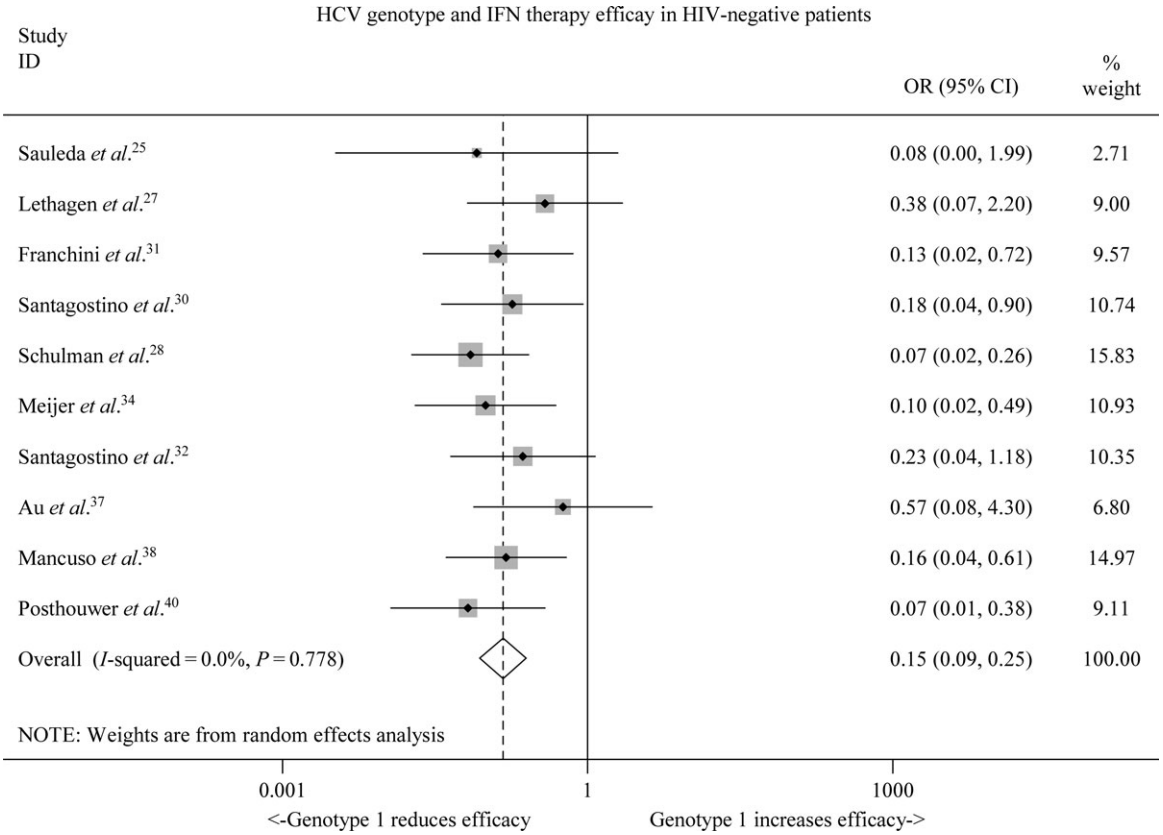

Figure 1. Pooled OR estimates and their 95% CI for the outcome sustained viral response in patients with genotype 1 compared with non-1 genotypes. Studies are identified by the first author. Size of squares is proportional to weighted OR.

Combination of Peg-IFN plus ribavirin was superior in terms of rate of SVR to the combination of non-Peg-IFN plus ribavirin (61% versus 43% in HIV-negative patients, Table 3), though this difference was not statistically significant by meta-regression (Table 4). Moreover, rates of SVR towards HCV genotype 1 infection were higher in patients treated with Peg-IFN compared

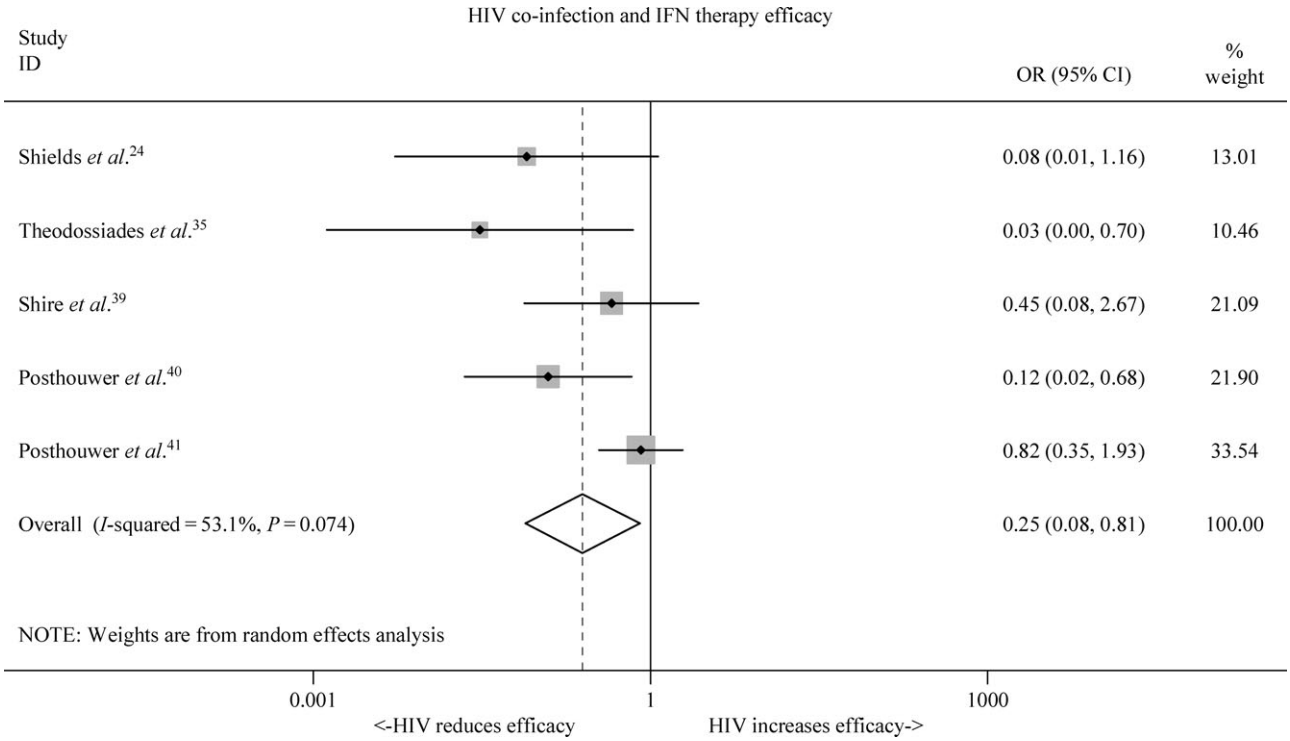

Figure 2. Pooled OR estimates and their 95% CI for the outcome sustained viral response in HIV-1-co-infected patients compared with patients with HCV infection only. Studies are identified by the first author. Size of squares is proportional to weighted OR.

with patients treated with non-Peg IFN (45% versus 34%), but they were substantially similar in patients with non-1 genotypes (77% in non-Peg-IFN treated and 79% in Peg-IFN treated). The effect of other variables (e.g. age at treatment, age at infection and duration of HCV infection) on response to treatment was not uniformly addressed across studies and could not be further analysed.

Visual examination of the funnel plot [Figure S1, available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/)] showed no evidence of publication bias, which was confirmed by the Begg and Mazumdar test.

Discussion

Many patients with haemophilia and other congenital bleeding disorders have been infected by HCV, which has become a significant cause of morbidity and mortality in this patient group.[1] Haemophiliacs therefore represent a unique model for studying the natural history of HCV infection and associated complications because the onset of the infection is known (the time of the first treatment with non-virus-inactivated blood products), and the course of hepatitis can be accurately assessed because these patients have usually had periodic laboratory, clinical and instrumental follow-ups over long periods in haemophilia centers.[42,43]

Literature data show that in many infected haemophiliacs, the liver disease has a mild, slowly progressing course.[2] These findings have been recently confirmed by Assy *et al.*[44] who compared liver histology from 12 haemophiliacs and 20 non-haemophilic controls with chronic hepatitis C and found significantly lower histological activity and fibrosis scores in haemophilic patients. The authors hypothesized the importance of thrombosis and vascular factor in the pathogenesis of HCV cirrhosis to explain the more benign course in haemophiliacs than in non-haemophiliacs.

In the present study, we evaluated whether, besides the previous documentation of a slowly progressive natural history of chronic hepatitis C,[2] haemophiliacs also had a favourable response to antiviral therapy.

Some limitations of our analysis should be acknowledged. First, we found few randomized controlled trials, as the majority of trials analysed were cohort studies. In this respect, meta-analysis of observational data is known to have more biases than meta-analysis of randomized controlled trials.[45] Nonetheless, we tried to provide more insights to the topic considering possible sources of heterogeneity between the results from observational studies. In particular, we attempted to evaluate the effect of combined treatment of HCV with IFN plus ribavirin comparing studies that involved cohort of patients who had haemophilia. However, outcome data were available in separate arms only according to genotype (genotype 1 versus others) and to HIV-1 infection status. The influence of other predictive variable was addressed by means of meta-regression.

In this systematic review, the first performed on HCV-infected haemophilic patients, we observed that the combination of Peg-IFN plus ribavirin was superior in terms of rate of SVR to the combination of non-Peg-IFN plus ribavirin (61% versus 43%), though this difference was not statistically significant by meta-regression. However, the relationship between SVR and type of IFN used, at least for non-1 genotypes, was not as clear as expected.

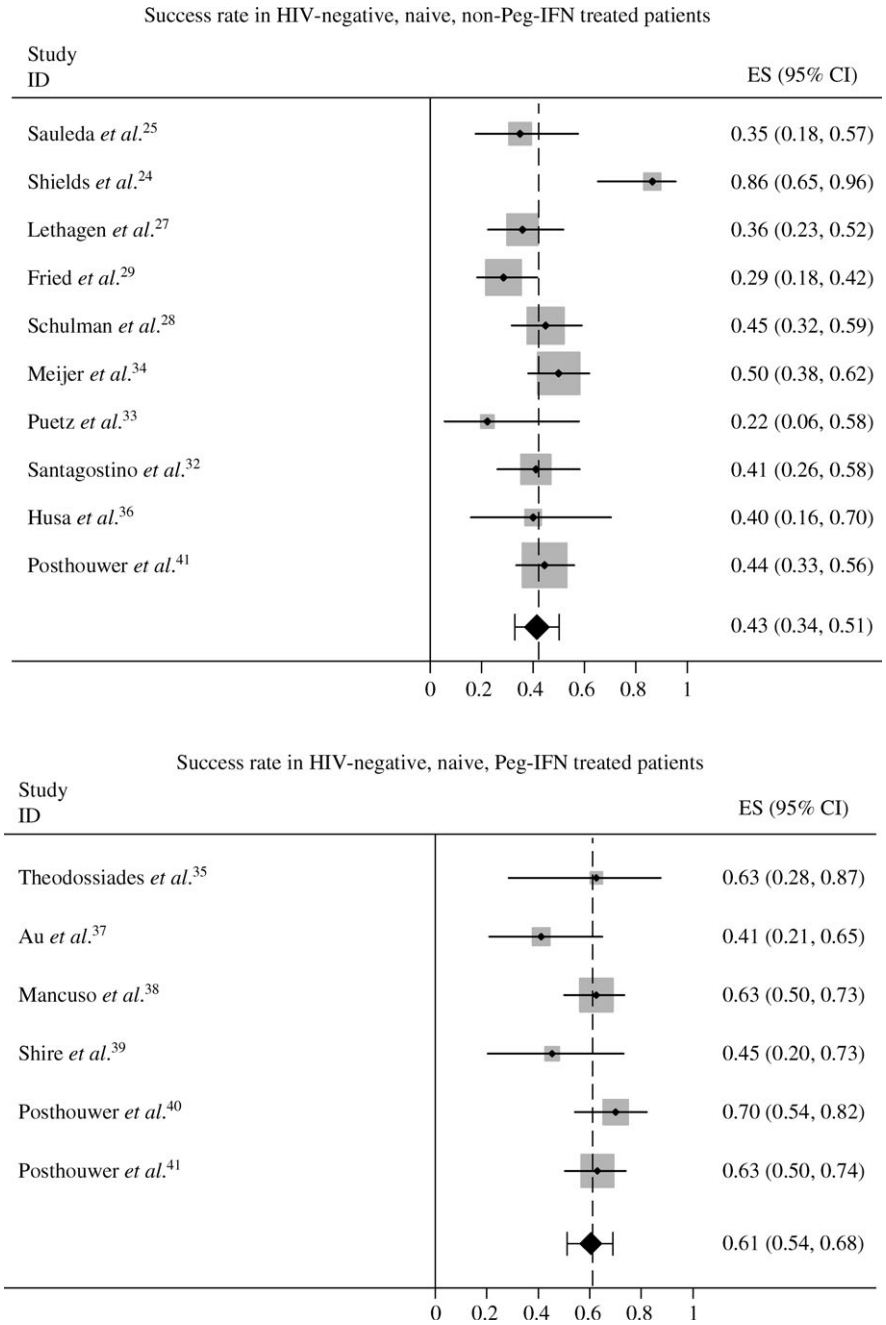

Figure 3. Summary random-effects weighted rates of sustained viral response and 95% CI in patients without HIV co-infection and IFN-naive. Top: subgroup of patients treated with non-Peg-IFN plus ribavirin. Bottom: subgroup of patients treated with Peg-IFN plus ribavirin. Studies are identified by the first author.

These results were comparable to those observed in the general population of HCV treated patients.[46] As observed in non-haemophilic patients,[47] genotype 1 (OR, 0.15; 95% CI, 0.09–0.25) and HIV-1 co-infection (OR, 0.25; 95% CI, 0.08–0.81) were strong predictors of worse response to IFN therapy. Pooled response rates observed with IFN plus ribavirin in HIV-co-infected haemophiliacs were comparable to rates in HIV-co-infected non-haemophilic patients from other meta-analyses.[48,49] These data also confirm for haemophiliacs the worse influence of HIV infection not only on the course of hepatitis C,[50] but also on the response to antiviral therapy.[51]

In conclusion, this meta-analysis documents that chronic hepatitis C in haemophiliacs has a behaviour similar to that in non-haemophilic patients both in terms of response to ribavirin plus IFN therapy and in terms of negative predictors of IFN therapy efficacy. The heterogeneity of treatment effect was explained by HCV genotype, HIV infection status and, to a lesser extent, to the type of IFN used. Also, the results in the general population of HCV-infected people are in agreement with the findings that a substantial percentage of HIV-co-infected haemophiliacs (up to 40%) can eradicate the HCV virus with combination antiviral therapy.

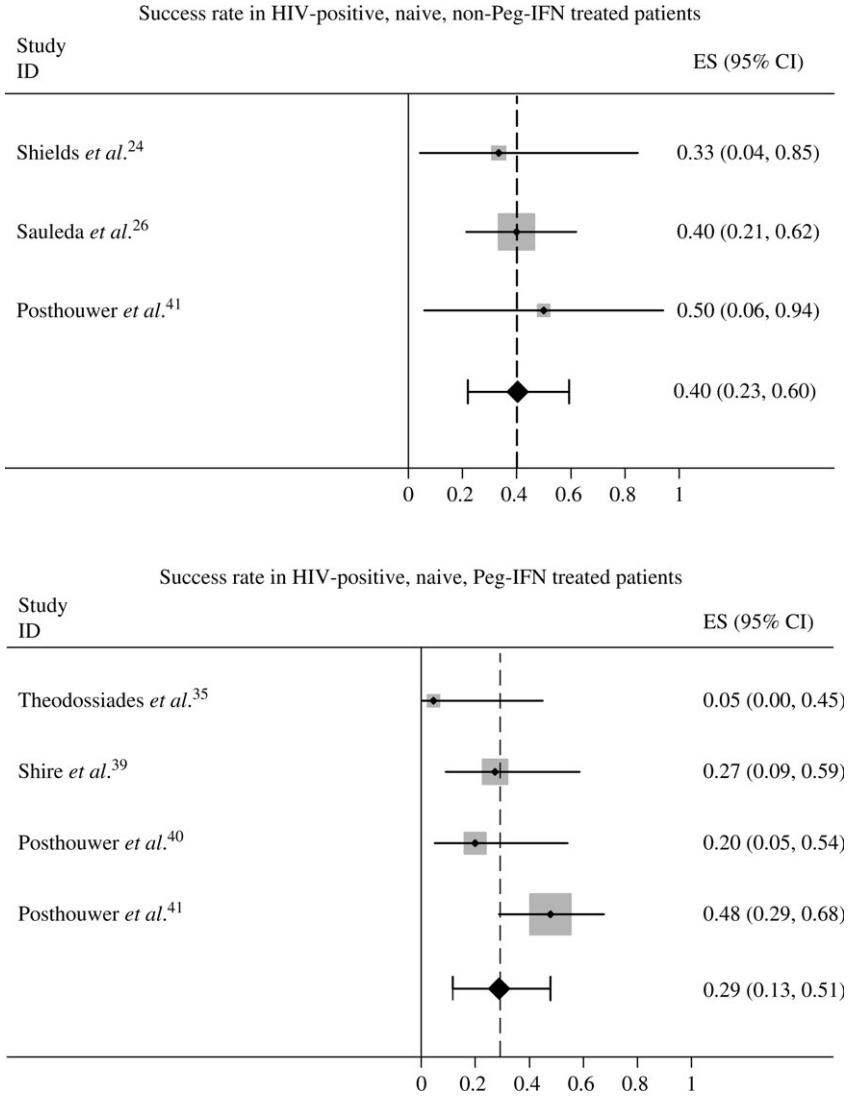

Figure 4. Summary random-effects weighted rates of sustained viral response and 95% CI in patients with HIV co-infection and IFN-naive. Top: subgroup of patients treated with non-Peg-IFN plus ribavirin. Bottom: subgroup of patients treated with Peg-IFN plus ribavirin. Studies are identified by the first author.

Table 4. Results of the random effects meta-regression, odds ratio estimates and heterogeneity assessment

				Heterogeneity assessment			
Variable	Class	Method	*P* value (t or z)[a]	*Q* (dof)	*P* value	I^2 (%)	τ^2
Type of IFN	Peg-IFN versus non-Peg-IFN in HIV-negative, naive patients	meta-regression	0.135	43.47 (12)	<0.001	72.4	0.3703
	Peg-IFN versus non-Peg-IFN in HIV-positive, naive patients	meta-regression	0.616	5.48 (5)	0.36	8.7	0.1405
	Peg-IFN versus non-Peg-IFN (all patients)	meta-regression	0.428	57.15 (19)	<0.001	66.8	0.364
Genotype	genotype 1 versus non-1 genotypes	odds ratio	<0.001	7.39 (11)	0.77	0.9	0
HIV infection	HIV-1 co-infection versus HCV infection only	odds ratio	0.019	9.03 (4)	0.06	55.7	0.978

dof, degrees of freedom.
The comparison between genotype 1 versus other genotypes, and between HIV-1-infected and uninfected patients was performed using a classical meta-analytical approach.
[a]*P* values are calculated from *t* values of meta-regression coefficient and from *z* values of OR.

Funding

No specific funding was received.

Transparency declarations

None to declare.

Supplementary data

Table S1 and Figure S1 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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