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Improved hepatitis C treatment response in younger patients: findings from the UK HCV National Register cohort study

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SUMMARY

In a cohort of 272 treatment-naive individuals with chronic hepatitis C infection acquired on a known date who were enrolled in the UK HCV National Register, a progressive improvement in response to treatment was found with the evolution of antiviral therapies from 20% (25/122) for interferon monotherapy to 63% (55/88) for pegylated interferon + ribavirin therapy. Multivariable analysis results showed increasing age to be associated with poorer response to therapy [odds ratio (OR) 0·84, 95% confidence interval (CI) 0·72–0·99, $P=0·03$] whereas time since infection was not associated with response (OR 0·93, 95% CI 0·44–1·98, $P=0·85$). Other factors significantly associated with a positive response were non-type 1 genotype ($P<0·0001$) and combination therapies ($P<0·0001$). During the first two decades of chronic HCV infection, treatment at a younger age was found to be more influential in achieving a sustained viral response than treating earlier in the course of infection.

Key words: Age at treatment, HCV, hepatitis C, treatment.

INTRODUCTION

Hepatitis C virus (HCV) is a global public health problem [1] and mathematical models suggest that there were around 190 000 individuals aged 15–59 years with antibodies to hepatitis C virus living in England and Wales in 2003 [2]. This equates to around 142 000 individuals in this age group living with chronic hepatitis C infection [2], many of whom will be asymptomatic and undiagnosed. Individuals with chronic HCV infection are at risk of cirrhosis and may progress to end-stage liver disease or liver cancer [3]. National data sources for transplants, deaths and hospital admissions in England, show that HCV-related end-stage liver disease is rising [2] and the number of people living with HCV-related cirrhosis or its complications is predicted to rise to over 10 000 by 2015 [4]. Current estimates suggest that around 9000 individuals were treated for hepatitis C infection in England in 2007 and 2008 [3]. If a higher number of HCV-infected individuals are not

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diagnosed and offered treatment, the future burden of disease on healthcare resources will be substantial.

There has been a steady improvement in response rates to antiviral therapy for chronic HCV infection over 15 years [5–8]. The current National Institute of Health and Clinical Excellence (NICE) recommended treatment of choice for chronic HCV is a course of pegylated interferon plus ribavirin (Peg-IFN + Rib) [9, 10]. Using this therapy, sustained viral response (SVR) has been reported in around 40–50% of those with genotype 1 infections, and around 75–80% of those with non-1 genotypes [7, 8]. However, it is unclear whether the response rates in routine clinical practice approach those achieved within the trial setting.

Several virus and host-related factors are reported to be associated with a lower virological response to therapy [11]. HCV genotype 1 and a high baseline viral load are the major viral factors associated with a lower response [7, 8]; patient-related factors include previous relapse or non-response to therapy [12–14], the presence of cirrhosis [15, 16], obesity [17] (although results are conflicting [11]), older age [15, 18], or a combination of these and other factors [11]. Those studies reporting an association between age at treatment and response have suggested that older HCV-infected patients may be more resistant to IFN-based therapies because they are more often infected with genotype 1b, have had the disease longer, or have more extensive liver damage than younger patients [11]. Knowing whether treatment is more successful if initiated at a younger age or earlier in the course of infection is important for counselling patients and for planning health services. At an individual level, this information is required when balancing the relative merits of 'watchful waiting' over early treatment, particularly when clinical indicators suggest that disease progression is mild. On a population basis, this information is also important when determining the most cost-effective way to invest in case-finding and treatment services. Uniquely, individuals who are enrolled in the HCV National Register have a known – not estimated – date of acquisition of infection [19], so it is possible to investigate the impact of duration of infection, and age at treatment, on the outcome of treatment. Further, many patients in the HCV National Register have had their liver biopsy referred to a central archive and scored by an independent consultant histopathologist blind to all clinical data [19], so that reliable information on the extent of liver damage is also available.

The aim of this study was to describe the response to antiviral therapy for HCV infection outside the trial setting and to investigate whether treatment response varies with the duration of infection or with age at the time of treatment.

METHODS

The UK HCV National Register contains data on a cohort of individuals who acquired their HCV infections on a known date and via a known route [19]. Case definitions, details of registration and follow-up protocols, and completeness of data are reported elsewhere, along with the methods used to maximize data quality [19]. Clinical data on these individuals are collected from healthcare settings throughout the UK every 2–3 years, according to a rigorous follow-up protocol; response rates to follow-up requests exceed 90%. Individuals are flagged in the NHS Central Registers to ensure follow-up is complete for all individuals who are registered for care in the NHS [19].

All individuals enrolled in the UK HCV National Register by the end of 2009 who had received at least one course of antiviral therapy were identified. Data on the age, sex, ethnic group (white *vs.* non-white), country of birth (UK *vs.* non-UK), body mass index (BMI) [(obese BMI $\geqslant 30$) *vs.* not obese BMI < 30)], diabetes (presence reported *vs.* not reported), alcohol consumption (graded according to nil, within recommended limits, above recommended limits, excessive; see next paragraph), route of acquisition of infection (vertical *vs.* transfusion), date of infection, HCV genotype, and details of treatment (dates of treatment, treatment type and response) were extracted from the Register database [19].

Alcohol consumption was classified according to the UK Department of Health's guidelines [20]. Men and women drinking more than 28 and 21 units, respectively, were classified as drinking above recommended limits. Individuals who drank more than twice the upper recommended number of units per week were classified as drinking excessively, along with those whose drinking was reported using subjective terminology indicating excess, like 'very heavy drinker', 'excessive', or 'alcoholic'. When alcohol consumption was reported as 'rare', 'occasional' or 'minimal', etc., consumption was coded as 'within recommend limits'. When alcohol consumption was not recorded for children, it was coded as 'nil' if they were aged < 10 years and as 'not known' if they were

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Table 1. *Baseline characteristics of the 272 eligible patients*

Characteristic	
Sex, *n* (%)	
Male	133 (48·9)
Female	139 (51·1)
Country of birth, *n* (%)	
UK	231 (84·9)
Non-UK	15 (5·5)
Not known	26 (9·6)
Ethnic group, *n* (%)	
White	238 (87·5)
Non-White	15 (5·5)
Not known	19 (7·0)
BMI, *n* (%)	
Obese (BMI $\geqslant 30$)	17 (6·3)
Not obese (BMI < 30)	111 (40·8)
Not known	144 (52·9)
Diabetes, *n* (%)	
Any report of diabetes	24 (8·8)
No mention of diabetes	248 (91·2)
Alcohol consumption*, *n* (%)	
Nil	62 (22·8)
Within recommended limits	155 (57·0)
Over recommended limits	20 (7·4)
Excessive	13 (4·8)
Not known	22 (8·1)
Route of acquisition, *n* (%)	
Transfusion	233 (85·7)
Vertical	33 (12·1)
Risk uncertain	6 (2·2)
Mean age at infection, years (S.D.)	27·0 (18·9)
HCV genotype, *n* (%)	
1	110 (40·4)
2	29 (10·7)
3	83 (30·5)
4	2 (0·7)
5	4 (1·5)
6	1 (0·4)
Not known/mixed	43 (15·8)
Mean age at first course of treatment, years (S.D.)	37·1 (19·0)
Duration of infection at first course of treatment, years (S.D.)	10·1 (4·7)

BMI, Body mass index; S.D., standard deviation.
* Classified according to UK Department of Health's guidelines [20].

older. Where more than one record of alcohol consumption was available for any individual, the highest recorded level was used in the analysis.

Response to a first course of therapy in treatment-naive patients was assessed. Most individuals would have been treated according to existing NICE guidance at the time, and within each regimen the guidance on specific treatment duration has not changed; no one was treated post-2010 when abbreviated abtiviral courses became recommended [10]. Individuals were classified as having gained a SVR to antiviral treatment if they remained negative for HCV RNA on PCR testing 6 months after completion of their first course of antiviral therapy.

Statistical analysis

Associations between variables and response to treatment were initially investigated using univariable analysis (*t* tests for continuous variables and χ^2 tests for categorical variables). A multivariable logistic regression model was then constructed with outcome of treatment (SVR *vs.* failure to achieve a SVR) as the dependent variable. The model was selected by initially including all variables with the exception of obesity (due to missing data) and age at infection (due to co-linearity as it is equal to age at treatment minus duration of infection). To increase precision of estimates, non-significant variables were dropped in a step-wise fashion with the exception of sex and the primary variables of interest, i.e. age at treatment and duration of infection.

Ethical approval

The UK National HCV Register cohort study was approved by the North Thames Multicentre Research Ethics committee (MREC: 98/2/47).

RESULTS

Sample

By the end of 2009, 321 of the 1176 patients enrolled in the HCV National Register with known dates of infection had received at least one course of antiviral therapy for HCV infection: 243 individuals received one course, 61 received two courses, 13 received three courses and four more than three courses.

Response to a *first course* of treatment was analysed in 272 individuals (five individuals were excluded because dates of treatment were unknown; 44 others were excluded because treatment was ongoing or had finished recently so that final treatment outcome could not be determined). Baseline characteristics of the sample are shown in Table 1; two individuals reported having *other* significant chronic viral infections, but details of these had not been disclosed.

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Table 2. *Treatment response according to treatment type and genotype in 231 treatment-naive individuals whose genotype was known*

Therapy type …	IFN monotherapy		IFN + Rib		Peg-IFN + Rib	
Genotype …	1	Non-1	1	Non-1	1	Non-1
SVR*, % (*n*)	6·8 (3/44)	26·5 (13/49)	26·5 (9/34)	66·7 (14/21)	37·5 (12/32)	78·4 (40/51)

IFN, Interferon; Rib, ribavirin; Peg-IFN, pegylated interferon.
* Sustained viral response: defined as testing negative for HCV RNA by PCR, 6 months after completion of antiviral therapy.

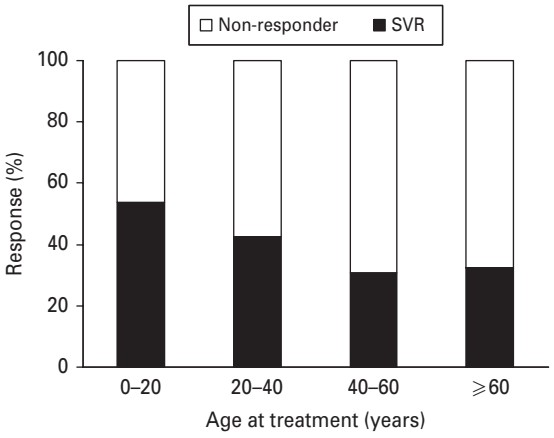

Fig. 1. Response to a first course of antiviral treatment by age when commencing treatment ($n=272$). SVR, Sustained viral response defined as testing negative for HCV RNA by PCR, 6 months after completion of antiviral therapy.

Response to a first course of antiviral therapy in treatment-naive patients

Treatment-naive individuals had received a variety of different antiviral therapies for their first treatment course; 122 received IFN monotherapy, 62 received IFN + Rib, and 88 received Peg-IFN + Rib.

Overall, 109 of 272 treatment-naive individuals achieved a SVR following the first course of antiviral therapy (40%). When response in treatment-naive individuals was stratified by treatment type, the overall response rates were: 20·1% (25/122) for IFN monotherapy, 46·8% (29/62) for IFN + Rib in combination, and 62·5% (55/88) for Peg-IFN + Rib.

For the subset of individuals for whom genotype was known ($n=231$), overall response rates to treatment were 21·8% (24/110) for genotype 1 and 55·4% (67/121) for non-1 genotypes. Treatment response by genotype for the different treatment types is summarized in Table 2.

Factors associated with a SVR following therapy

Univariable analyses showed that those who responded to treatment ($n=109$) were more likely to be younger at infection (mean 22·2 years *vs.* 30·2 years, $P<0·001$; see Fig. 1), younger when they started treatment (mean 33·3 years *vs.* 39·6 years, $P=0·007$), to have a longer duration of infection (mean 11·2 years *vs.* 9·4 years, $P=0·003$), more likely to have had combination therapy, particularly with Peg-IFN ($P<0·001$), more likely to have acquired HCV infection vertically ($P=0·02$), less likely to have diabetes reported ($P=0·01$), and be more likely to have non-1 genotypes ($P<0·001$) compared to those who did not respond ($n=163$). Response to treatment did not differ significantly by sex ($P=0·46$), country of birth ($P=0·84$), ethnic group ($P=0·20$), alcohol consumption ($P=0·37$) or BMI ($P=0·11$).

The multivariable logistic regression model, fitted to look at the independent effects of age at treatment and duration of infection on treatment outcome, included these variables as well as sex and the significant variables viral genotype and antiviral therapy type (Table 3). The model shows that those who were treated at a younger age were significantly more likely to achieve a SVR following antiviral therapy than those undergoing therapy at older ages. Duration of infection at treatment did not have an independent significant effect on treatment response. Predicted response rates, from the model, to a course of Peg-IFN + Rib therapy are shown for patients aged 20 and 60 years in Figure 2.

DISCUSSION

This study of 272 treatment-naive individuals with chronic HCV infection found a 40% response rate to a first course of antiviral therapy. There was

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Table 3. *Multivariable logistic regression analysis with outcome of treatment (SVR* vs. no SVR) as the outcome variable (n = 272)*

Variable	OR (95% CI)	*P* value
Age at treatment (per 10 years)	0·84 (0·72–0·99)	0·03
Duration of infection at treatment (per 10 years)	0·93 (0·44–1·98)	0·85
Sex (male *vs.* female)	1·38 (0·77–2·45)	0·28
Treatment type		
IFN + Rib *vs.* IFN monotherapy	5·66 (2·51–12·77)	< 0·0001
Peg-IFN + Rib *vs.* IFN monotherapy	9·23 (3·90–21·80)	< 0·0001
Genotype:		
1 *vs.* non-1	0·16 (0·08–0·32)	< 0·0001
Unknown *vs.* non-1	1·18 (0·52–2·71)	0·69

OR, Odds ratio; CI, confidence interval; IFN, interferon; Rib, ribavirin; Peg-IFN, pegylated interferon.
* SVR: defined as testing negative for HCV RNA by PCR, 6 months after completion of antiviral therapy.

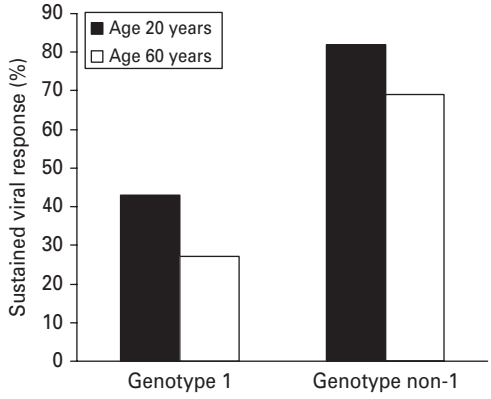

Fig. 2. Model predicted response rates to a first course of pegylated interferon and ribavirin therapy in individuals with chronic HCV. Sustained viral response defined as testing negative for HCV RNA by PCR, 6 months after completion of antiviral therapy.

improvement in response rates with the evolution of antiviral therapies from 20·1% (IFN monotherapy) to 62·5% (Peg-IFN + Rib). Initial therapy with Peg-IFN + Rib ($n = 83$) resulted in a SVR for 78·4% of individuals with non-1 genotypes and 37·5% of individuals with genotype 1. HCV genotype and therapy type were both significant independent predictors of response to a first course of antiviral therapy.

There was no evidence to suggest that treatment in the first decade of infection achieved a better response rate than treatment in the second decade of infection, after controlling for the evolution of therapy types with time and other confounding factors. The association between duration of infection and treatment response that was observed in the univariable analysis did not remain in the multivariable analysis, after controlling for the confounding influence of better therapies in more recent years. The study shows that a SVR was more likely if antiviral therapy was commenced at a younger age. It is recognized that early treatment of acute hepatitis C prevents chronic infection in most patients [21]. However, acute infection is usually asymptomatic, and more commonly observed as seroconversion in risk groups who are serially tested, or following occupational exposure to the virus. Once chronic infection has become established, as for the individuals in this cohort and most others who are not serially tested, treatment at a younger age seems to be more influential in achieving a SVR than treating early in the course of infection. However, none of the individuals in the multivariable analysis had been infected for more than 25 years at the time of first treatment and it is likely that duration of infection exerts a greater influence in the third decade of infection when severe histological disease and cirrhosis are more common.

The HCV National Register is a database which was established in 1998 and represents one of the largest contemporary cohorts of known date HCV-infected individuals in Europe [19]. It contains anonymized data on more than 1170 HCV-infected individuals in the UK who acquired HCV infection on a known date and by a known route. An unusual feature of the Register is that it is a national cohort involving patients who were mostly asymptomatic when identified and therefore recruitment was independent of disease progression [19, 22]. As patients are included based on exposure rather than disease, the register provides a cohort of HCV-infected individuals which encompasses the full clinical spectrum and is not over-represented by those with severe illness. It also benefits from including infections acquired from different virological sources [19, 23, 24].

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Information on clinical, demographic and other potential confounding factors was relatively complete; the exception was information on obesity (47·1% complete), which was not significantly associated with response to therapy in univariable analyses. BMI increases with age and has been associated with a reduced response to antiviral therapy [17], yet when BMI was included in the multivariable model with an additional category for 'BMI missing' the odds ratios for the other variables remained similar despite there being some evidence of a reduced odds of successful treatment in those categorized as obese (OR 0·37, 95% CI 0·08–1·79). Of the 321 cases identified as receiving at least one course of antiviral therapy, only five (1·5%) were excluded as a result of missing data. Since 1998, follow-up with the responsible clinician has occurred about every 2–3 years and losses to follow-up are negligible as all individuals are flagged in the NHS Central Registers [19, 25].

Because age at infection and age at treatment are highly correlated, it is inherently difficult to establish whether higher rates of SVR are the result of a better age-specific response to therapy or because individuals who acquired their infections at a younger age respond better to treatment because their disease has progressed more slowly. However, when re-running the final multivariable model for the subset of 145 patients with liver biopsy fibrosis staging within 2 years of starting treatment (staged by an independent histopathologist blinded to outcome), the age at treatment effect was sustained after adjusting for disease progression at the time of treatment. Age-related differences in response to treatment may be explained by age-specific differences in the immune response, which may be a result of a decrease in the number and function of naive T cells [26], alterations in cytokine profile and shifts in the ratios of naive *vs.* memory T-cell populations [27, 28] or immune senescence [29].

Most cases in the series were transfusion recipients (85·7%) traced through a national look-back exercise; HCV acquired vertically contributed to 12·1% of the study population. This does not reflect the pattern of HCV acquisition in the UK, where most infections are acquired via injecting drug use [3]. As transfusion recipients are more likely to have co-morbidity [30, 31] and patients with a history of injecting drug use are likely to differ in other important ways, including alcohol use, this may limit general application of the findings [30, 31].

In this study of treatment-naive individuals, response rates to the current therapy of choice (Peg-IFN + Rib) suggested that for those with genotype 1 infections, response rates fell slightly short of those achieved in clinical trials (38% *vs.* 40–50%), whereas for those with non-1 genotypes, responses to treatment were in line with those achieved in trial settings (78% *vs.* 75–80%) [7, 8].

Age is an important factor [15, 18] but as it can act as a surrogate for disease duration, the ability to identify the precise date of infection and adjust for duration of infection has provided a rare opportunity to disentangle the influence of each factor on treatment response. The finding of a reduced response to treatment with age is supported by data from meta-analyses and large, randomized clinical trials of combination therapy with IFN-α or Peg-IFN + Rib. Age >40 years was identified as an independent predictor of a reduced SVR [7, 8, 32, 33]. In a retrospective study of 153 adult patients from a hospital-based cohort, patients aged $\geqslant 40$ years had a significantly lower chance of achieving a sustained response compared to younger patients (adjusted OR 0·16, 95% CI 0·05–0·59) [34]. However, the retrospective design of the study and the use of hospitalized cases are important biases that limit its general application.

These findings are particularly relevant for healthcare planners in the UK, where at least 8000 newly identified infected individuals have been reported each year, almost double the number treated in the same period [3]. Data from the HPA 2009 HCV Annual Report highlight the significant contribution made by injecting drug users to the burden of chronic HCV in the UK [3]. Between 1996 and 2008, 50% of laboratory reports of HCV infection occurred in individuals aged between 20 and 39 years; where risk factor information was available, more than 90% reported injecting drug use as a risk. Combination therapy with Peg-IFN + Rib is a cost-effective intervention and economic evaluations suggests that treating younger individuals with mild disease does fall below the £30 000 cost per quality-adjusted life year threshold adopted by NICE in England and Wales [35, 36].

Although recent public health efforts rightly focus on preventing new infections, increasing awareness and increasing diagnosis, these findings suggest that, diagnosing and treating individuals at a younger age can have an impact on improving response to the current combination treatment of choice. Furthermore, treatment at an older age is associated with increased drug intolerance, particularly with ribavirin, resulting in reduced adherence to therapy [34, 37, 38].

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'Watchful waiting' of individuals with mild disease may come at a cost if response rates fall as individuals age.

While needle-exchange schemes and near patient testing facilities are important in identifying infected individuals in the community, treatment at a younger age will also contribute to reducing the burden of disease. Efforts should therefore focus on raising awareness of these benefits in primary and secondary care as part of the overall strategy to control hepatitis C in the UK.

The logistics of treating the increasing numbers of individuals diagnosed with chronic HCV infection will be challenging, and it is important that all patients have access to high-quality care. Because the long-term effects of ribavirin and Peg-IFN in children are still to be defined, it is important that children continue to be seen in specialist tertiary centres. For others, service provision in the community may increase access to care, but it is critical that provision of antiviral therapy in the community is safe, clinically and cost-effectively, and of equal quality to that delivered in tertiary centres. Out-reach services would need to be managed by an appropriate specialist and patients treated in the community would need equal access to support services that meet the differing needs of different patient groups. Managed multidisciplinary clinical networks that monitor outcomes and inform commissioning will be the key to developing high-quality local services that are accessible to all. This will be particularly important with the imminent availability of more effective, but expensive, antiviral treatments whose indications for use will need to be clearly defined to ensure the best use of scarce resources.

NOTE

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org/hyg).

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DECLARATION OF INTEREST

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