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The efficacy and safety of treating hepatitis C in patients with a diagnosis of schizophrenia

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SUMMARY. Treating chronic hepatitis C with pegylated interferon alpha may induce or exacerbate psychiatric illness including depression, mania and aggressive behaviour. There is limited data regarding treatment in the context of chronic schizophrenia. We sought to establish the safety and efficacy of treating patients with schizophrenia. Patient and treatment data, prospectively collected on the Scottish hepatitis C database, were analysed according to the presence or absence of a diagnosis of schizophrenia. Time from referral to treatment, and the proportion of patients commencing treatment in each group, was calculated. Outcomes including sustained viral response rates, reasons for treatment termination and adverse events were compared. Of 5497 patients, 64 (1.2%) had a diagnosis of schizophrenia. Patients with schizophrenia (PWS) were as likely to receive treatment as those without [28/61(46%) vs 1639/4415 (37%) $P = 0.19$]. Sustained viral response (SVR) rates were higher in PWS [21/25 (84%) vs 788/1453 (54%) $P < 0.01$]. SVR rates by genotype were similar [4/8 (50%) vs 239/684 (35%) Genotype 1 ($P = 0.56$), 17/17 (100%) vs 599/742 (81%) non-Genotype 1 ($P = 0.09$)]. Adverse events leading to cessation of treatment were comparable [2/25(8%) vs 189/1453 (13%) P: 0.66]. Patients with schizophrenia are good candidates for hepatitis C treatment, with equivalent SVR and treatment discontinuation rates to patients without schizophrenia.

Keywords: hepatitis C, pegylated interferon alpha, schizophrenia.

INTRODUCTION

Chronic hepatitis C virus infection (HCV) is a significant public health problem in Scotland with an estimated 39 000, or 0.8% of the population, being afflicted [1]. Schizophrenia is a common psychiatric disorder with an estimated population prevalence of 0.5% in the United Kingdom [2]. Seroprevalence of HCV in severe mental illness (schizophrenia, bipolar disorder and major depression) has been shown to be as high as 19.6% [3]. Other studies have revealed HCV prevalence rates of 4.1% amongst patients with schizophrenia (PWS) [4].

Treating HCV with pegylated interferon alpha (IFNα) may induce or exacerbate psychiatric illness including depression, mania and aggressive behaviour [5]. Its use in patients with a history of severe psychiatric conditions is recommended only after appropriate psychiatric management.

The potential to exacerbate underlying psychiatric illness may deter clinicians from treating PWS. A US veteran's cohort study identified increasing age, substance abuse, major and minor depression, bipolar disorder and schizophrenia as independent predictors of nontreatment for HCV [6]. Despite this, limited data suggest that PWS treated with IFNα experience psychiatric symptoms at comparable rates to untreated controls [7], [8]. Supporting this, sustained viral response rates have been shown to be similar [8] or better [9] amongst PWS compared to controls.

We sought to establish the safety and efficacy of treating PWS attending treatment centres in Greater Glasgow.

METHODS

We conducted a retrospective analysis of patient and treatment data prospectively collected on the Scottish HCV database between early 1992 and April 2012, for patients

Abbreviations: HCV, hepatitis C virus; IFNα, interferon alpha; IQR, interquartile range; PWS, patients with schizophrenia.

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Table 1 Baseline characteristics of patients with hepatitis C

Characteristic	Patients with schizophrenia	Controls	Total	*P* value
Total number of patients, *n*	64	5433	5497	
Mean age in years	36 ± 7.8	35 ± 7.2		0.26
Male gender (%)	53 (83)	3845 (71)	3898 (71)	0.04
Race (%)				
Caucasian	64 (100)	5120 (94.2)	5184 (94.3)	0.08
Black	0	24 (0.4)	24 (0.4)	0.62
Asian	0	249 (4.6)	249 (4.6)	0.15
Others	0	40 (0.7)	40 (0.7)	0.93
Alcohol excess (%)	25 (39)	1211 (22)	1236 (22)	0.002
Intravenous drug abuse (%)	50 (78)	3015 (55)	3065 (56)	<0.01
Patients with cirrhosis (%)	13 (20)	597 (11)	610 (11)	0.03
HCV genotype (%)				
1	26 (50)	1462 (43)	1488 (43)	0.31
2	1 (1.9)	184 (5)	185 (5)	0.35
3	25 (48.1)	1742 (51)	1767 (51)	0.76
4	0	34 (1)	34 (1)	0.92

attending Greater Glasgow treatment centres. Data were analysed according to the presence or absence of schizophrenia.

Data on demographic characteristics, severity of liver disease, genotype, prior alcohol excess, substance abuse, time from referral to first attendance and first attendance to treatment were collected. Those treated with combination antiviral therapy (IFNα and ribavirin) were identified, and outcomes including sustained viral response (SVR), discontinuation rates and adverse events were collected.

Database entries were supplemented with case note review to collect data on mental health history and reasons for delay or deferral of treatment amongst PWS. Patients with a diagnosis of drug-induced psychosis were excluded from the analyses. Standard practice across our treatment centres during the period studied was to offer treatment to patients evaluated as stable by their treating psychiatrist.

Statistical analysis was undertaken using MedCalc software. Categorical variables were analysed using chi-square or Fisher's exact test as appropriate. Continuous variables were compared using the *t* test or Mann–Whitney *U* test. Normally distributed continuous data are presented as mean (±standard deviation, SD). Nonnormally distributed continuous variables are presented as median (interquartile range, IQR).

RESULTS

A total of 5500 patients were recorded on the database, of whom three were excluded due to a diagnosis of drug-induced psychosis. Of 5497 patients, 64 (1.2%) had a diagnosis of schizophrenia. Patients were predominantly male (83%) with a mean age of 36 ± 7.8 years. Baseline characteristics of PWS and controls were similar (Table 1), with the exception of higher rates of current or former intravenous drug use, prior alcohol excess and cirrhosis. A total of 1700 patients were treated, with PWS as likely to undergo treatment as controls [28/61(46%) vs 1639/4415 (37%), $P = 0.19$]. Amongst treated patients (Table 2), PWS were older [mean 46 ± 7.4 vs 37 ± 7.2 $P < 0.01$] and more likely to be cirrhotic [9/28 (32%) vs 265/1639 (16%), $P = 0.04$].

9/28 (32%) of PWS undergoing HCV treatment received Olanzapine as treatment for their schizophrenia, with 18 patients on other treatments (four Quetiapine, four Amisulpride, four Risperidone, two Aripiprazole, two Zuclopenthixol, one Flupentixol and one unspecified depot treatment). Review of medical case notes was unable to identify psychiatric medication in one patient.

A total of 192 patients (three PWS and 189 controls) not yet 6 months posttreatment were excluded from treatment outcome analysis. Overall SVR rates were higher in PWS [21/25 (84%) vs 788/1453 (54%), $P < 0.01$], analysis per genotype showed similar SVR rates amongst genotype 1[4/8 (50%) vs 239/684 (35%) $P = 0.56$) and genotype 2/3 infected patients [17/17 (100%) vs 599/742 (81%) $P = 0.09$). Treatment discontinuation due to adverse events (Table 3) was similar [2/25 (8%) vs 189/1453 (13%), $P = 0.66$], with no difference in discontinuation due to depression [1/25 (4%) vs 27/1453 (1.8%), $P = 0.95$]. No patient discontinued treatment due to worsening schizophrenia. No PWS discontinued therapy due to noncompliance (0/25 (0%) vs 72/1453 (5%), $P = 0.49$).

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Table 2 Baseline characteristics of patients commenced on antiviral therapy

Characteristic	Patients with schizophrenia	Controls	*P* value
Patients commenced on antiviral therapy *n* (%)	28/61 (46)	1639/4415 (37)	0.189
Mean age in years	46 ± 7.4	37 ± 7.2	<0.01
Male gender (%)	23 (82)	1147 (70)	0.24
Race (%)			
Caucasian	28 (100)	1425 (85)	0.05
Black	0	10 (0.6)	0.40
Asian	0	188 (11)	0.12
Others	0	16 (1)	0.66
Alcohol excess (%)	10 (36)	348 (21)	0.09
Intravenous drug abuse (%)	18 (64)	668 (41)	0.02
Patients with cirrhosis (%)	9 (32)	265 (16)	0.04
HCV genotype (%)			
1	9 (33)	721 (44)	0.33
2	0	93 (5.6)	0.38
3	19 (67)	803 (49)	0.08
4	0	22 (1.2)	0.76

Table 3 Adverse events leading to cessation of treatment amongst patients with schizophrenia and controls

Side effects	Patients with schizophrenia (n = 25)	Controls (n = 1453)
Depression	1 (4%)	27 (1.8%)
Thrombocytopenia	0	14 (0.96%)
Anaemia	0	13 (0.9%)
Flu like symptoms	0	8 (0.5%)
Thyroid disorders	1 (4%)	2 (0.1%)
Weight loss	0	2 (0.1%)
Leucopenia	0	1 (0.06%)
Others	0	68 (4.6%)
Missing	0	54 (3.7%)

PWS took longer from referral to treatment [1217 (609–2025) vs 535 (278–1315) days, $P < 0.01$]. A minority of both PWS and controls commenced treatment within 1 year of referral [4/28 (14%) vs 534/1639 (32%) $P = 0.06$]. Comparing the first and last 3 years of the study, referral to treatment times fell amongst both PWS (2990 (1186–4794) vs 605 (185–902), $P = 0.08$) and controls (746 (429–1333) vs 262 (167–445), $P < 0.01$). In the last 3 years studied, referral to treatment time was not significantly longer amongst PWS (605 (185–902) vs 262 (167–445), $P = 0.23$).

Patient factors (poor attendance, unstable drug and alcohol use, unstable schizophrenia, significant co-morbidities) accounted for the majority of delays in progressing to treatment amongst PWS (21/25, 84%). Delays in receiving psychiatric assessment were uncommon [2/25 (8%)]. Two patients initially not offered treatment (one due to mild disease and one receiving Clozapine) were subsequently treated on follow-up.

DISCUSSION

Tolerability of interferon amongst PWS is of significance given a higher rate of HCV infection within this group. Approaching one in five adults tested amongst a sample of 931 patients with severe mental illness attending US inpatient and outpatient psychiatric facilities were found to have HCV [3]. Screening of patients treated with Clozapine, an atypical antipsychotic reserved for patients with refractory schizophrenia, revealed a prevalence of 4.1% [4]. Prevalence rates of HCV amongst PWS are higher than controls even in the absence of a self-reported history of substance misuse [10].

Our cohort demonstrates PWS to be good candidates for treatment with interferon containing regimens. It is well tolerated, with only 4% of PWS discontinuing treatment due to psychiatric illness. Despite a rate of cirrhosis twice that of controls, SVR rates were numerically higher amongst both genotype 1- and genotype 2/3-infected PWS.

This intriguing finding is not unique, with a prior study showing a higher SVR rate amongst genotype 2/3 PWS compared with controls [9]. We hypothesize that this may be explained by better compliance with treatment. Amongst our PWS, none discontinued treatment due to the lack of compliance with prescribed medication. Those PWS undergoing treatment had been identified by their treating psychiatrist as stable, and this may in part be due to good compliance with prescribed psychiatric medication. The increased time from referral to treatment amongst PWS may reflect closer scrutiny of likelihood of treatment success, including compliance. Thus, the PWS we treat are likely a selected cohort with good compliance. We suggest that the well-established relationship between compliance and SVR rates [11,12] may explain our better than expected SVR rates amongst PWS.

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In addition to the effects of patient selection on compliance, there is evidence to show that PWS and concomitant diabetes demonstrate improved compliance with oral hypoglycaemic medications [13], and have lower HbA1c levels [14], than matched diabetic controls without schizophrenia. This may be as a result of frequent contact and supervision by community psychiatric nurses. Studies involving direct observed therapy in patients with HCV showed a greater proportion of patients achieving SVR [15], and one may speculate that psychiatric input designed to aid compliance with antipsychotic medication may have a similar effect. A weakness of our study is a lack of data on the degree of psychiatric support and whether this was predictive of achieving SVR, an area worthy of further research.

Whilst clinical trials of new interferon-free regimens have classified PWS as ineligible for treatment with interferon [16], there is no convincing data to support this. Whilst these regimens are likely to be better tolerated, cost dictates that they will not be available to all and we would advocate not excluding PWS from treatment with Interferon.

In conclusion, given the disproportionately high rates of chronic hepatitis C in PWS and the good SVR rates reported, we suggest that targeted treatment for this patient group can be safely considered.

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DISCLOSURE

None.

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