New direct-acting antivirals for hepatitis C treatment and neuropsychiatric symptoms in psychiatric risk groups

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ABSTRACT

Objectives The new direct-acting antivirals (DAAs) have changed chronic hepatitis C virus (HCV) treatment perspectives by achieving success rates in all genotypes and by reducing the associated adverse effects in comparison to pegylated interferon α regimens. These adverse effects include depression, insomnia and suicidal intention, which make it difficult to treat psychiatric risk groups. The objectives of this study were to evaluate the neuropsychiatric symptoms during HCV treatment with DAAs in standard multidisciplinary clinical practice in psychiatric risk groups and to assess the risk factors associated with neuropsychiatric symptoms in this study population.

Methods A prospective cross-sectional study was performed of all consecutive patients with psychiatric risk and HCV infection who completed treatment with the new DAAs at the ambulatory care pharmacy. We recorded demographic and clinical data, neuropsychiatric symptoms, emergency consultations, admissions to the psychiatric unit and interventions to manage neuropsychiatric symptoms. Statistical analysis was used to assess the association between neuropsychiatric symptoms and clinical data.

Results We included 48 patients with psychiatric risk and detected 36 neuropsychiatric symptoms in 17 (35.4%) patients, with a mean of 0.75 neuropsychiatric symptoms per patient. However, no studied risk factors for developing neuropsychiatric symptoms were found in this population.

Conclusions We found a moderate prevalence of neuropsychiatric symptoms in the psychiatric risk group. The neuropsychiatric symptoms more frequently reported were insomnia (17%), irritability (15%) and depression (13%). Neuropsychiatric symptoms in patients with psychiatric risk can occur during treatment with DAAs but less frequently than with pegylated interferon α regimens, and so is a safe treatment for these patients.

INTRODUCTION

The global prevalence of chronic hepatitis C virus (HCV) is estimated at 2.5% (177.5 million adults with HCV infection).¹ A significant number of those who are chronically infected will develop liver cirrhosis or liver cancer and approximately 700 000 people die each year from hepatitis C related liver diseases.^{2,3} Among the six HCV genotypes, the most prevalent is genotype 1.⁴

Until 2011, the standard treatment for patients with HCV infection was interferon α (IFN α) along with ribavirin, achieving success rates in genotype

1 of approximately 45–50% and for all genotypes over around 54%.^{5,6} However, a contraindication of this regimen is depression since treatment with pegylated IFN α can induce neuropsychiatric side events, such as depression, in 25–40% of all patients undergoing IFN α therapy for HCV.^{5,7–12} Furthermore, according to Sockalingam *et al*, ‘HCV-infected patients with pre-existing psychiatric disorders may have an exacerbation of a secondary psychopathology related to IFN α ’,¹³ and ‘the onset of suicidal ideation and suicide during HCV therapy in general population coincide with the onset of IFN α -induced neuropsychiatric symptoms (IFN α -D)’.^{14,15} Nevertheless, no data regarding the prevalence of neuropsychiatric symptoms in patients with psychiatric risk are available.

In addition, substance use disorders and psychiatric morbidity are significantly more prevalent in patients with chronic hepatitis C (CHC) than in the general population.¹⁶ The reason could be because they are associated with an increased risk of infection, and emerging evidence suggests that they can also be related to the infection itself.¹⁷ Sixty percent of patients with HCV infection have a history of psychiatric disease and nearly 90% have a history of substance use disorders.¹⁸ Moreover, as stated by Bini *et al*, ‘patients with psychiatric illness and substance use disorders have higher rates of not being treated for HCV infection (OR for psychiatric illness, 9.45; OR for a substance use disorder, 17.68), despite the fact that their rates of treatment completion and sustained virological response are similar to those of patients without these comorbidities’.¹⁹

Nevertheless, major changes to this clinical concern began with the development of the first direct-acting antivirals (DAAs). US Food and Drug Administration (FDA) prescribing information for recent drugs, that are FDA approved, do not note psychiatric symptoms as recognised side effects.²⁰ Clinical trial ‘data indicate that these no interferon-alpha/no ribavirin regimens are far more well tolerated by patients, do not seem to have notable psychiatric contraindications and the type of psychosocial assessment for these regimens are typical in medical care’.⁷

Therefore, with these recently FDA-approved DAA treatments for HCV without IFN α and ribavirin, treatment settings no longer seem to need to have strong psychosocial and monitoring assessment. However, some exclusion criteria of the studies assessing efficacy and security of the

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new DAAs included patients 'with any psychiatric hospitalisation, suicide attempt, psychiatric disability period in the recent 5 years, current or recent alcohol and/or substance abuse', as reported by Afdhal *et al.*²¹

Enhanced post-commercialisation monitoring with the DAA regimens will allow clinicians to gain experience in patients with psychiatric comorbidities. These regimens seem to be well tolerated in patients with psychiatric comorbidities.²² Consequently, if this statement is confirmed in the future and evidence comes in, it could extend the number of patients eligible to initiate DAA regimens,²³ and we will no longer need close psychosocial assessment and patient monitoring in those undergoing HCV treatment.²³

Although the introduction of DAAs for HCV treatment seems to have decreased the neuropsychiatric symptoms in patients with psychiatric risks, there are some further research issues to be assessed for these recently approved regimens. The aims of this study are to evaluate the neuropsychiatric symptoms that occur during HCV treatment with DAAs in standard multidisciplinary clinical practice in patients with psychiatric risk, and to assess the risk factors associated with neuropsychiatric symptom presentation in this population.

METHODS

Study design

We performed a prospective study of all consecutive patients with HCV infection and psychiatric diagnosis or receiving treatment with psychiatric medication who completed DAA treatment at the ambulatory care pharmacy in coordination with the liver unit and the infectious disease unit at Mataró Hospital (Barcelona, Spain) from February 2015 to December 2016. Mataró Hospital is a general hospital with 350 beds, which covers a sanitary area that attends to approximately 265 000 inpatients of which approximately 2% have HCV.²⁴

All patients with IFN-based treatment or patients participating in ongoing clinical trials were excluded.

We recorded demographic data (age, sex), HIV coinfection, HCV genotype, fibrosis stage, baseline viral load, prior HCV treatment, data about actual HCV treatment (regimen and duration), alcohol and substance drug use, and psychiatric disorders before treatment, including irritability and depression. Main outcome measures of psychiatric disorders were evaluated in relation to severity, management and outcome. We also recorded all neuropsychiatric symptoms, emergency consultations, admissions to the psychiatry unit during the treatment and interventions to manage neuropsychiatric events (medication prescriptions, lifestyle modifications or temporal or definitive treatment interruptions) during and after the treatment according to the DAA treatment.

Data regarding adherence and sustained viral response (SVR) were also recorded.

Inclusion criteria

We included all patients with psychiatric disorders and/or in treatment with psychiatric medication and/or who had had a psychiatric medical visit before the treatment. We considered antidepressants, benzodiazepines, antipsychotics, mood stabilisers and stimulants as psychiatric medication.

Exclusion criteria

Exclusion criteria were patients with IFN-based treatment, those with DAAs without completing the treatment for any reason

except for neuropsychiatric symptoms, and patients participating in ongoing clinical trials.

Hepatic fibrosis

Hepatic fibrosis was measured by FibroScan. Fibrosis stage was defined as mild (Metavir score F0–F1) if stiffness ≤ 7.1 kPa; moderate (F2) if 7.2–9.4 kPa; severe (F3) if 9.5–14 kPa, and cirrhosis (F4) if > 14 kPa.²⁵

Adherence

Adherence to treatment is critical for success in HCV therapy and failed therapy may select for resistant variants, affecting future treatment options.²⁶ We have defined adherence in line with Farmer *et al* as 'the extent to which the patient's history of therapeutic drug-taking coincides with the prescribed treatment at least 50%'.²⁷ We evaluated adherence by pill counts at the 4-week pharmacy visits when patients bring their 4-week pill boxes, which has shown higher accuracy when compared with other subjective methods.²⁷ In the first visit, the patients were not aware of pill counts, but in the next visits (one if it was an 8-week regimen, two if it was a 12-week regimen and four if it was a 24-week regimen), they were aware. The adherence was measured as the percentage of pill count against the number of pills prescribed.

Neuropsychiatric symptoms

Evaluation data of neuropsychiatric symptoms secondary to DAAs were taken from psychopathological explorations in the clinical history according to CIE criteria 10, including depression, irritability, dream alterations, psychotics, mania and obsessive disorders (these have also been described in the literature during treatment with IFN). Moreover, the severity of the neuropsychiatric symptoms was determined based on clinical criteria and the *Diagnostic and statistical manual of mental disorders* (fifth edition).²⁸

Sustained viral response

We evaluated SVR because it is the most widely used efficacy endpoint of HCV treatment, which is defined as undetectable HCV RNA (≤ 15 IU/mL) in serum using a sensitivity test at 24 weeks after completion of antiviral treatment.^{29 30}

Data analysis

We calculated the mean and SD for the quantitative variables and the frequency and percentage for the estimation of the qualitative variables. To compare the means of a quantitative variable in the groups of a dichotomous qualitative variable, we used the Student t test, and to compare categorical variables, we used the χ^2 test. To compare the means of a quantitative variable in the groups of a qualitative variable of more than two categories, we used the ANOVA test. The P values corresponded to the statistical significance of bilateral tests. Results were considered statistically significant with a P value of < 0.05 in the study population. The statistical software SPSS 19 was used.

RESULTS

We evaluated 173 patients with HCV in treatment with the new DAAs, of which 48 were receiving treatment with psychiatric medication, had psychiatric disorders and/or had a psychiatric medical visit before the treatment. Exclusion criteria are summarised in online supplementary table 1. Briefly, 157 patients completed the treatment with the new DAAs and were not participating in ongoing clinical trials, but 109 were

Table 1 Demographic characteristics and clinical data of patients with HCV and psychiatric risk receiving treatment with DAAs

Patients (n=48)	N (%)
Age (mean)	52±23 (42-75)
Women	12 (25)
Genotype	
1a	19 (39.6)
1b	17 (35.4)
2	1 (2.1)
3	3 (6.3)
4	7 (14.6)
Fibrosis (kPa)	
F0-1	2 (4.2)
F2	4 (8.3)
F3	14 (29.2)
F4	26 (54.2)
Not available	1 (2.1)
Pretreatment	
Naive	36 (75.0)
INF	3 (6.3)
INF+RBV	6 (12.5)
Telaprevir+INF+RBV	2 (4.2)
SIM+SOF	1 (2.1)
HCV/HIV coinfectd	26 (54.2)
Treatment	
SOF±ORB	1 (2.1)
SOF+SMV±ORB	7 (14.6)
SOF+LDV±RBV	34 (70.8)
SOF+DCV±RBV	3 (6.3)
OMB/PAR/RTV+DAS±RBV	3 (6.3)
Weeks	
8	6 (12.5)
12	22 (45.8)
24	10 (20.8)
Changes before treatment	12 (5.0)
Drug abuse	
Metadone	12 (25.0)
Cocaine	1 (2.1)
Alcohol	4 (8.3)
Cannabis	3 (6.3)
Adherence (%)	96
Sustained viral response	48 (100)
All adverse drug events	
Tiredness	20 (41.7)
Dermatological disorders	11 (22.9)
Gastrointestinal disorders	7 (14.6)
Myalgia	5 (10.4)
Headache	5 (10.4)
Syndrome flu-like	3 (6.3)
Loss of appetite	2 (4.2)
Dizziness	1 (2.1)
Neuropsychiatric symptoms	
Insomnia	8 (16.7)
Irritability	7 (14.6)
Depression	6 (12.5)
Excessive sleepiness	4 (8.3%)
Aggression	3 (6.3%)
Psychotic disorder	3 (6.3%)

Continued

Table 1 Continued

Patients (n=48)	N (%)
Attention deficits	2 (4.2%)
Hallucinations	2 (4.2%)
Suicidal ideation	1 (2.1%)
Psychiatric medication changes during treatment	
Drug prescription	6 (12.5%)
Dose reduction	3 (6.3%)
Dose increase	2 (4.2%)
Treatment change	1 (2.1%)
Stop drug	1 (2.1%)
Emergency/psychiatric consultations	2 (4.2%)
Hospital admissions	2 (4.2%)

DAA, direct acting antiviral; DAS, dasabuvir; DCV, daclatasvir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INF, interferon; LDV, ledipasvir; OMB/PAR/RTV, ombitasvir/paritaprevir/rtonavir; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.

not considered patients with psychiatric risk as defined in the inclusion criteria. [Table 1](#) shows baseline clinical and treatment characteristics and online supplementary table 2 shows clinical data of patients with HCV according to the DAA treatment. We considered antidepressants, benzodiazepines, antipsychotics, mood stabilisers and stimulants as psychiatric medication.

Clinical data

All 48 (100%) included patients with psychiatric risk had SVR, and adherence was high, as the median pill count was 27 of a total of 28 pills for the 4-week treatment (96%). See online supplementary table 2 which shows the adherence according to the regimen used. Neuropsychiatric symptoms had no influence on treatment adherence or SVR in the multivariate analysis.

Neuropsychiatric symptoms

During treatment with the new DAAs, 36 neuropsychiatric symptoms were detected in 17 of 48 patients (35.4%) with psychiatric risk and of all 157 (10.8%) patients reviewed, with a mean of 0.75 neuropsychiatric symptoms per patient. The neuropsychiatric symptoms more frequently reported were insomnia in 8 patients (16.7%), depression in 7 (14.6%), irritability in 6 (12.5%) and drowsiness in 4 (8.3%). Two patients (4.2%) had severe or life-threatening neuropsychiatric symptoms and had to be admitted to the psychiatric unit.

Psychiatric medication changes

Prescription of psychiatric medication was needed or required adjustment in 13 patients (27.1%) during HCV treatment: medication was started in 6 patients (12.5%) and dose was adjusted in 5 patients (10.4%). The psychiatric treatment was stopped in 1 patient (2.1%) and changed to another drug in another patient (2.1%). Prescribed psychiatric medication during HCV treatment was distributed as follows: 3 patients (6.25%) received benzodiazepines as hypnotics, 2 patients (4.2%) received antipsychotics and 1 patient (2.1%) received benzodiazepines as anxiolytics.

Hospital admissions

Two patients (4.2%) were admitted to the psychiatric unit for mental health symptoms. Both were also receiving treatment for HCV for 24 weeks. One of these patients, after 2 months of being in treatment with sofosbuvir and simeprevir, had hallucinations and suicidal ideations. These adverse drug events associated with the HCV treatment were evaluated by the Naranjo

algorithm,³¹ which indicated the relationship between the drug and the development of neuropsychiatric symptoms was 'probable' (Naranjo scale=5). In the case we describe, HCV treatment preceded the delusions and the autolytic intention. We excluded other drugs because the effect appeared only after the use of the DAA regimen.

In the other case, the neuropsychiatric symptom, which was a psychotic disorder, appeared the week before finishing the HCV treatment with sofosbuvir and ledipasvir. Again, it was evaluated by the Naranjo algorithm, which indicated the relationship between the drug and the development of neuropsychiatric symptoms was 'probable' (Naranjo scale=5).

Risk factors for neuropsychiatric symptoms

Predictor variables included in the univariate analysis of baseline risk factors for neuropsychiatric toxicity included gender, age, HIV coinfection, HCV genotype, fibrosis stage, baseline viral load, prior HCV treatment, regimen and duration of HCV treatment, alcohol and drug use and psychiatric disorders before

treatment, including irritability and depression. As shown in table 2, any of the study factors was statistically significantly associated with neuropsychiatric toxicity in patients with psychiatric risk after the bivariate analysis ($P>0.05$). However, the most frequent clinical factors of confusion found in patients with neuropsychiatric symptoms were genotype 2, 3 and 4, previous treatment with telaprevir+IFN+ ribavirin, coinfection with HIV, treatment with sofosbuvir, simeprevir±ribavirin, duration of treatment of 24 weeks and use of other substances of abuse.

DISCUSSION

This prospective study of a cohort of patients with HCV treated with the new DAA regimens provides comprehensive information about the prevalence and course of neuropsychiatric symptoms occurring during antiviral therapy, which could be relevant for the management of these complications.

In our study we found a moderate prevalence of neuropsychiatric symptoms in the psychiatric risk group and a minority of patients receiving DAA treatment had severe or life-threatening

Table 2 Baseline characteristics of patients with and without neuropsychiatric symptoms in patients with psychiatric risk, n (%)

Patients (n=44)	Neuropsychiatric symptoms (n=16)	No neuropsychiatric symptoms (n=32)	P value	OR (95% CI)
Age (years), median±IQR	51.6±6.42	53.7±10.52	0.818	0.97 (0.91 to 1.05)
Women	3 (18.8%)	9 (28.1%)	0.725	0.59 (0.14 to 2.57)
Genotype				
1a	5 (31.3%)	13 (40.6%)	0.753	0.53 (0.19 to 2.37)
1b	5 (31.3%)	13 (40.6%)	0.753	0.53 (0.19 to 2.37)
2, 3, 4	6 (37.5%)	6 (18.8%)	0.178	2.16 (0.68 to 9.99)
Fibrosis (kPa)				
F0, F1, F2, F3	7 (43.8%)	15 (46.9%)	1.000	1.00 (0.30 to 3.35)
F4	9 (56.3%)	17 (53.1%)	1.000	1.13 (0.34 to 3.80)
Pretreatment				
Naive	11 (68.8%)	25 (78.1%)	0.500	0.62 (0.16 to 2.37)
INF+RBV	3 (18.8%)	6 (18.8%)	1.000	1.00 (0.22 to 4.65)
Telaprevir+INF+RBV	1 (6.3%)	1 (3.1%)	1.000	2.07 (0.12 to 35.4)
SOF+SMV	1 (6.3%)	0	0.333	ND
Viral load>800 000 IU/mL	11 (68.8%)	23 (71.9%)	1.000	0.86 (0.23 to 3.19)
HCV/HIV coinfectd	11 (68.8%)	13 (40.6%)	0.125	3.22 (0.90 to 11.5)
Treatment				
SOF+SMV±RBV	4 (25.0%)	3 (9.4%)	0.201	3.22 (0.62 to 16.63)
SOF+LDV±RBV	11 (68.8%)	23 (71.9%)	1.000	0.86 (0.23 to 3.19)
Others (SOF±RBV, SOF+DCV±RBV, OMB/PAR/RTV+DAS±RBV)	1 (6.3%)	6 (18.8%)	0.398	0.29 (0.03 to 2.63)
Weeks				
8	1 (6.3%)	5 (15.6%)	0.357	1
12	10 (62.5%)	22 (68.8%)	-	0.89 (0.23 to 22.10)
24	5 (31.3%)	5 (15.6%)		5.00 (0.42 to 59.7)
Nervous system treatment (ATC codes)				
Antiepileptics (N03)	3 (18.8%)	5 (15.6%)	1.000	1.25 (0.26 to 6.03)
Anti-parkinson drugs (N04)	2 (12.5%)	1 (3.1%)	0.254	4.42 (0.370 to 52.99)
Antipsychotics (N05A)	4 (25.0%)	11 (34.4%)	0.742	0.64 (0.166 to 2.45)
Anxiolytics (N05B)	7 (43.8%)	15 (46.9%)	1.000	0.88 (0.26 to 2.95)
Hypnotics and sedatives (N05C)	2 (12.5%)	0 (0%)	0.106	ND
Psychoanaleptics (N06)	6 (37.5%)	10 (31.3%)	0.750	1.32 (0.38 to 4.65)
Other nervous system drugs (N07)	5 (31.3%)	7 (21.9%)	0.500	1.62 (0.042 to 6.26)
Drug abuse				
Metadone	7 (25.0%)	5 (31.3%)	0.732	0.56 (0.35 to 5.31)
Other drug abuse (cocaine, heroine, cannabis, alcohol)	6 (37.5%)	4 (14.3%)	0.133	3.60 (0.83 to 15.6)

DAS, dasabuvir; DCV, daclatasvir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INF, interferon; LDV, ledipasvir; ND, no data; OMB/PAR/RTV, ombitasvir/paritaprevir/ritonavir; RBV, ribavirine; SMV, simeprevir; SOF, sofosbuvir.

neuropsychiatric symptoms in comparison with all patients treated with the new DAAs in our centre. However, the seriousness of these conditions highlights the relevance of their detection and prevention.³²

The neuropsychiatric symptoms more frequently reported in our study were insomnia, irritability and depression, and were mainly managed with a prescription, dose increase or dose reduction of the psychiatric medication. Remarkably, no patient required drug interruption or dose reduction of HCV treatment. In a large trial¹² over 52 weeks of all patients in treatment with pegylated IFN α -2b, the rate of insomnia was 40%, irritability was 35% and depression was 31%. In another study by Fried *et al*, 'rates of other depression-related symptoms for pegylated IFN α -2b were fatigue (64%) and weight loss (29%)'.⁵ However, the rate of insomnia with pegylated IFN α -2a over 48 weeks was 37%, irritability was 24% and depression was 22%.⁵

In this study, no risk factor for neuropsychiatric symptoms was found after the statistical analysis. This could be explained by the low number of patients due to the recent introduction of the new DAAs (we have data from February 2015) and because it was a single centre study. These factors limited our ability to include more patients to find statistical differences. However, the most frequent clinical factors of confusion found in our patients with neuropsychiatric symptoms were genotype 2, 3 and 4, previous treatment with telaprevir+IFN+ribavirin and coinfection with HIV.

As for the chronology of the neuropsychiatric symptoms, we observed that they can occur from a few weeks to the end of the treatment.

Moreover, we need to highlight the high percentage of patients who achieved SVR (100%) and the high adherence of these patients as a result of strict control by pharmacists and nurses, who carried out 4-week visits to the patients with HCV, strengthening the importance of HCV treatment adherence.

Our results cannot be compared with previous studies because, to the best of our knowledge, no other study has been conducted studying the relationship between neuropsychiatric symptoms and DAAs post commercialisation. Some previous studies have studied the effect of new DAAs on HCV and, secondarily, their effect on neuropsychiatric symptoms. However, some exclusion criteria of these studies included 'patients with any psychiatric hospitalisation, suicide attempt, or recent psychiatric disability period and current or recent alcohol or substance abuse', as stated by Afdhal *et al* and Ferenci *et al*.^{21 22}

Therefore, the present study confirms that neuropsychiatric symptoms, which are life-threatening complications in the era of IFN regimens, has now changed this clinical concern with the approval of the new DAAs. However, further studies in this field are needed.

Our study characterises neuropsychiatric symptom occurrence during DAAs therapy in HCV psychiatric-risk patients. We have demonstrated that although neuropsychiatric symptoms are not frequent with DAAs treatments they can also occur. The main implication of this finding is that they can be used in patients with a history of psychiatric disease and substance use disorders, but psychosocial assessment and monitoring them for drug interactions with psychiatric medication and for neuropsychiatric symptoms are equally required during the HCV treatment.

Nevertheless, there are several limitations to this work that limited our ability to establish a causative link between any risk factor and neuropsychiatric symptoms. First, this was a prospective cross-sectional study performed at a single site. However, the prospective design in combination with computerised medical record allowed for accurate measure of the hepatitis

C treatment exposure and systematic assessment of matching variables. Second, the study would have benefited from more subjects. Despite the low number of subjects due to the recent introduction of the new DAAs and for being a single centre study, which limited the ability to find statistical differences, this study provides valuable results to identify the occurrence of neuropsychiatric symptoms during new DAAs treatments in psychiatric patients. To address the limitations of this study and determine if the new hepatitis C treatments are causally associated with neuropsychiatric symptoms, future prospective studies can randomise larger number of subjects.

In conclusion, in our cohort of psychiatric-risk patients receiving the new DAAs treatments in real life conditions, the neuropsychiatric symptoms were not common but have to be taken into account. Multidisciplinary management is needed to achieve an early detection and accurate control of these symptoms, preventing discontinuation of HCV treatment and maintaining SVR. No risk factors for neuropsychiatric symptoms during DAAs treatment for HCV have been able to identify in this study, but further prospective studies could determine which patients are eligible for DAAs therapeutic options, thus optimising health system resources.

What this paper adds

- The new direct acting antivirals (DAAs) for the HCV treatment seem to have decreased the neuropsychiatric symptoms associated with pegylated interferon-alpha (IFN α) regimens in psychiatric risks patients, but no prospective study has been performed in this group.
- We have found that, in real life conditions, the neuropsychiatric symptoms in our cohort of psychiatric-risk patients receiving the new DAAs were not as frequent as with the pegylated IFN α regimens, but they have to be taken into account.

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Competing interests None declared.

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