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The Addition of Vitamin D Supplementation to Interferon and Ribavirin in the Treatment of Hepatitis C Virus Infection: A Randomised Double-Blind Placebo-Controlled Pilot Study

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Abstract

***Background:** Vitamin D is known to be involved in the immune response to hepatitis C virus infection and preliminary data suggests that supplementation may improve response to treatment with interferon and ribavirin.*

***Methods:** The ViaDUCT study was a pilot, multi-centre, randomised, double-blind, placebo-controlled, parallel group clinical trial. Participants with hepatitis C who were planned for treatment were recruited and were randomised to 100,000 units oral vitamin D3 supplementation or placebo each month whilst undergoing treatment with interferon and ribavirin-based regimens. The primary outcome was sustained virologic responseat 12 weeks. Secondary outcomes were to identify the proportion of patients who dropped out and to assess for any increase in treatment-related toxicity. Study analyses were performed by modified intention to treat of the primary outcome which was compared between the two arms using logistic regression.*

***Results:** 72 participants were randomised; 35 to vitamin D and 37 to placebo. The mean age of participants was 42.5 and 41.7 years respectively. The majority of trial participants were male - 25 (71%) in the vitamin D arm and 24 (65%) in the placebo arm. Following treatment, 60 (83%) attended for assessment of sustained virologic response at 12 weeks. Sustained virologic response was achieved in 82.9% (95%CI 67.3-91.9%) in the vitamin D arm and 73.0% (95%CI 57.0-84.6%) in the placebo arm. The odds of sustained virologic response at 12 weeks in the intervention arm was not significantly greater than in the placebo arm (adjusted odds ratio 1.74; 95%CI 0.43-6.97, p= 0.44). Adverse events were in keeping with the expected side effect profile of interferon and ribavirin based regimens.*

***Conclusion:** Vitamin D supplementation did not significantly improve sustained virologic response when added to interferon and ribavirin-based treatment. The apparent effect size observed would require a largertrial to establish any true effect of this adjunctive therapy.*

***Trial Registration:** ClinicalTrials.gov Identifier: NCT02053519, URL: https://clinicaltrials.gov/ct2/show/NCT02053519, East of Scotland Research Ethics committee: 13/ES/0116*

Keywords: *Vitamin D, Interferon, Ribavirin, Hepatitis C virus*

Introduction

Hepatitis C virus (HCV) infection is a major global health issue. Recent models estimate a global prevalence of 1% indicating that over 70 million individuals are currently affected with millions of new infections occurring annually[1]. Infection often leads to chronic hepatitis and ultimately may proceed to cirrhosis, hepatocellular carcinoma and death[2].

The therapeutic landscape for HCV has evolved dramatically in recent years advancing from interferon and ribavirin-based regimens to multiple, novel, direct-acting antiviral agents. These novel regimens are expensive and access remains problematic for many individuals affected by HCV[3]. For example, a course of sofosbuvir costs $84,000 in the United States[4]. Many low and middle-income countries are, therefore, likely to continue to rely upon interferon and ribavirin based treatment protocols until generic manufacturing is permitted or access deals are agreed between governments and manufacturers [3] – a process that may take many years. Ways to maximise the efficacy of interferon/ribavirin regimes are therefore likely to be needed, especially in the short to medium term, if lower and middle income countries are to mount an affordable response to the public health challenge posed by hepatitis C infection.

Vitamin D is a term used to describe several fat-soluble compounds which play an important role in calcium homeostasis and an increasingly recognised role in immune function. Most of the required vitamin D is produced by the action of ultraviolet B radiation on the skin, with only a small contribution from dietary sources. Levels of circulating vitamin D metabolites are therefore often low in populations living at high latitudes, or in people with little exposure to sunlight due to other reasons, e.g. illness or conservative dress codes[5]. Associations between low circulating 25-hydroxyvitamin D (25OHD) levels and a wide range of illnesses have been noted, including malignancy, respiratory infection, autoimmune and cardio-metabolic diseases and notably, chronic liver disease including chronic HCV infection[6, 7].

The interplay between vitamin D and chronic liver disease has been further investigated in recent years. It has been demonstrated that 25OHD levels are lower in those with more severe liver dysfunction[8]. Interestingly it has also been shown that vitamin D levels rise following successful clearance of HCV infection [9]. The T-cell response against the virus may also rely upon vitamin D suggesting that deficiency may impair the immune response [10, 11]. Given the key role of the liver in the 25-hydroxylation of vitamin D however, observational studies cannot dissect out whether low 25OHD levels are a contributor to, or an effect of hepatitis C infection.

Preliminary clinical data does however suggest that vitamin D status is associated with response to treatment for HCV. In a small study in Italy *Bitetto et al* found that low 25OHD levels were associated with a poorer response to interferon and ribavirin and that supplementation increased the likelihood of response[12]. Both *Abu-Mouch et al* and *Nimer et al* performed randomised controlled trials in Israeli cohorts to establish if vitamin D supplementation affected SVR[13, 14].

The *Abu-Mouch et al* trial randomised 72 individuals with HCV genotype 1 to treatment with interferon/ribavirin with or without vitamin D supplementation. They found that vitamin D supplementation increased SVR in comparison to the control group, 86% vs 42% ($p<0.001$)[14]. In the *Nimer et al* trial, of 50 individuals with genotypes 2 and 3 infections, vitamin D supplementation was also associated with a significant increase in SVR,95% vs 77% ($p<0.001$) [13]. SVR was assessed at 24 weeks in these trials as was the then standard of care.

None of these previous studies were placebo-controlled and none were performed in northern European populations – who are those most likely to have low 25OHD levels[5]. We therefore performed a randomised, placebo-controlled pilot trial in Scotland, UK to more rigorously assess the hypothesis that vitamin D supplementation would improve SVR when added to an interferon and ribavirin based treatment regimen.

Methods

General Study Design and Plan

ViaDUCT was a pilot, multicentre, double blind, randomised, placebo controlled, parallel group trial to examine the effect of year-long course of monthly oral vitamin D3 treatment or placebo, on SVR rates in patients with HCV infection treated with interferon and ribavirin. As this was a pilot trial an important

measure was to determine the number of eligible individuals consenting to enter a trial of this design as well as the rate of recruitment. The trial was approved by East of Scotland Research Ethics committee (13/ES/0116), and Clinical Trials Authorisation was given by the UK Medicines and Healthcare Regulatory Authority (EudraCT number 2013-003573-10). The trial was registered at www.clinicaltrials.gov, registration number NCT02053519

Population

Individuals were recruited from viral hepatitis clinics in 5 health boards across the National Health Service in Scotland: NHS Tayside, NHS Greater Glasgow and Clyde, NHS Grampian, NHS Forth Valley and NHS Lothian. Inclusion criteria were: patients with known HCV infection confirmed by positive PCR, hepatitis C genotype 1 or 3, and planned to commence on standard HCV therapy, which at the time of trial recruitment was interferon/ribavirin based therapy.

The exclusion criteria were based upon the usual standard-of-care contraindications for treatment with interferon and ribavirin. In addition those at risk of, or known to have, hypercalcaemia were excluded due to the endocrine effects of vitamin D supplementation. The exclusion criteria were: hepatitis C genotype other than 1 or 3, contraindications to interferon or ribavirin therapy, estimated GFR <30ml/min/1.73m^2 (by MDRD4 method) [15] currently decompensated liver disease characterised by ascites, encephalopathy or variceal bleeding, history of renal calculi, serum calcium <2.15 or >2.60 mmol/L, history of sarcoidosis or metastatic malignancy, hepatocellular carcinoma, taking >400 international units of vitamin D per day, HIV positive, pregnancy, breastfeeding, of childbearing age and not on reliable contraception, or unable to provide written informed consent.

Participant Recruitment

At the screening visit all participants had their medical history taken and gave written informed consent. Confirmation of HCV diagnosis by viral load by polymerase chain reaction (PCR) and viral genotype was taken from the last available values in the medical notes.

Standard Treatment

Standard HCV therapy with interferon and ribavirin was commenced 1-4 weeks after the first dose of vitamin D or placebo. Standard treatment for HCV was 24 weeks. Genotype 1 patients who did not respond to therapy at week 4 or 12 had all anti-viral therapy stopped. Other genotype 1 patients who did respond but did not become virus negative at 12 weeks of therapy were continued on a further 24 week course of standard therapy, total duration 48 weeks. Those who did not respond and stopped antiviral therapy did not continue to receive vitamin D or placebo for the planned 12 month course in this trial. Those participants who continued on 48 weeks of standard therapy received the same 12 months of vitamin D or placebo but returned at 3 and 6 months post-end of treatment for assessment.

Standard therapy for HCV changed as the trial was performed and therefore some patients received additional antivirals concomitantly with interferon and ribavirin. Genotype 1 patients at the outset of the study received interferon/ribavirin but later patients could also receive telaprevir, boceprevir, simeprevir or sofosbuvir at their prescribing physician's discretion. Similarly, Genotype 3 patients at trial outset received interferon/ribavirin but later patients could also receive sofosbuvir.

Trial Treatment, Randomisation and Blinding

After successful confirmation of eligibility including safety, participants were randomised by the delegated nurse to either vitamin D3 or placebo in a double-blind fashion via a centrally controlled web-based GCP compliant randomisation system, run by Tayside Clinical Trials Unit (TCTU) to preserve allocation concealment. Randomisation was minimised for age (≤ 40, > 40) and genotype (1 or 3).

Oral vitamin D3 or matching placebo was administered once a month. Each dose of vitamin D3 or placebo was ingested by the participant in the presence of the study nurse. Participants were allowed to continue all their usual medication throughout the trial. The dose of vitamin D3 used was 100,000 units once a month (given as 5mls of Vigantoloil per dose [Merck KgAA]). Placebo was 5mls of Mygliol oil per dose; also provided by Merck KgAA; Mygliol is a medium-chain triglyceride used as the base oil in the manufacture of Vigantol. Vitamin D and placebo were identical on visual inspection and taste, and were dispensed from study bottles with no external indication of whether the bottle contained vitamin D or placebo. Participants,

research nurses recording outcomes, and healthcare teams thus remained blinded to treatment allocation.

Trial Outcomes

The primary outcome of the trial was the absence of detectable virus in blood, using PCR to detect HCV RNA, at 12 weeks, termed sustained virologic response (SVR12). This is a recognised surrogate marker for the cure of infection. In this trial any record of a negative HCV RNA 12 weeks or more after completion of treatment was taken as achievement of SVR12. Conversely a positive result was taken as failure of SVR12. In the absence of an HCV RNA result, for the modified intention to treat analysis, the participant was assumed to have failed to achieve an SVR.

Secondary outcomes were to identify the proportion of eligible patients undergoing therapy for HCV infection who drop out and to assess the effect of supplementation with Vitamin D on adherence to standard therapy. The number of individuals recruited by each site and the rate of recruitment over the 18 month study period was also recorded (February 2014 to August 2015). This data was to establish recruitment variability across sites and help to inform a calculation regarding the required recruitment period for a future large study. A further secondary outcome was to assess for any increase in the expected toxicity of therapy.

Sample Size Calculation

We estimated that a definitive trial would require 313 participants in each arm (assuming alpha=0.05 and beta=0.80) to have 80% power to show an improvement in SVR from 70% in the placebo group to 80% in the vitamin D group, at an alpha level of 0.05. The purpose of this pilot trial was not to detect this difference, but to estimate the likely effect size and recruitment rates to ensure that a future definitive trial was adequately powered. The sample size was therefore set at a maximum of 100 patients (50 randomised to each arm); this sample size was also deemed sufficient to demonstrate the ability of each of the study centres to recruit and retain subjects in the study, another key point for the pilot to address. This would enable the feasibility of a future larger study to be fully evaluated.

Statistical Analysis

Study analyses were performed by modified intention to treat (mITT) of the primary outcome SVR at 12 weeks. The evaluable dataset were those randomised and receiving at least one dose of vitamin D3 or placebo, with those with missing values for SVR assumed to have not achieved SVR. The primary outcome (SVR12) was compared between the two arms utilising logistic regression stratified by centre with a parameter indicating arm of trial. The primary analysis was an adjusted analysis, adjusting for baseline age, sex, genotype, 25OHD level and viral load. Further analyses were performed without adjustment for baseline variables, and using a per-protocol approach (excluding those who did not attend for SVR measurement). Subgroup analyses were not performed in view of the small numbers in the trial; such analyses would carry a high risk of spurious positive findings.

A 2-sided p value of <0.05 was taken as significant for all analyses. All analyses were conducted using SAS v9.3 by trial statisticians blind to treatment allocation.

Results

72 participants underwent randomisation and received the first dose of study medication. 35 were randomised to the vitamin D arm and 37 to the placebo arm. Flow through the trial is shown in Figure 1. 14 of the 35 (40%) in the vitamin D arm had a genotype 1 infection with the remainder having genotype 3 infection. 14 of the 37 (38%) in the placebo arm had genotype 1 infection with the remaining 23 having genotype 3 infection.

All received interferon/ribavirin therapy, however, within the vitamin D arm four genotype 3 participants also received sofosbuvir. Of genotype 1 participants, one received telaprevir and another boceprevir, three also received sofosbuvir and a further three received simeprevir. Within the placebo arm eight genotype 3 participants received sofosbuvir and among the genotype 1 participants, one received boceprevir and six received simeprevir. Of the 72randomised participants, 60 (83%) had a blood test performed for HCV RNA 12 weeks after end of trial medication to allow confirmation of achievement of SVR12. Baseline details are given in Table 1.

Table 1. *Baseline characteristics of study participants*

	Vitamin D	Placebo
N	35	37
Mean age (years) (SD)	42.5 (11.6)	41.7 (8.7)
Male sex (%)	25 (71%)	24 (65%)
Genotype 1 (%)	14 (40%)	14 (38%)
Genotype 3 (%)	21 (60%)	23 (62%)
Mean 25OHD level (nmol/L) (SD)	59 (24)	51 (21)
Mean HCV RNA level (x10^6 IU/ml) (SD)	2.5 (5.4)	1.2 (1.4)

25OHD: 25-hydroxyvitamin D. HCV: Hepatitis C virus

Changes in 25 OHD Levels across ViaDuct Trial

In the Vitamin D intervention group the mean change (averaged across all months) in 25OHD levels was +16.7 nmol/L (SD 39.5) compared to the placebo group where the mean change (averaged across all months) was -7.9 nmol/L (SD 21.8). The between-group difference was 24.7 nmol/L (95% CI 12.2 to 37.2; p<0.001 by Student's t-test)

Primary Outcome

The proportion of positive outcome (SVR at 12 weeks) was 82.9% (95% CI 67.3 – 91.9%) in the vitamin D group, and 73.0% (95% CI 57.0 – 84.6%) in the placebo group. The logistic regression analysis showed no significant difference between treatment and placebo (adjusted odds ratio = 1.74; 95% CI 0.43-6.97; p= 0.44). A breakdown of the primary outcome by genotype and antiviral therapy is available in Table 2.

The results were consistent between the adjusted and unadjusted logistic model (Unadjusted odds ratio = 1.79; 95%CI 0.57-5.60; p=0.32) which were further confirmed by a Chi-Square test on the proportion of positive SVR12 per treatments (p=0.31). A per protocol analysis was also performed as a sensitivity analysis and this also showed no significant difference in the SVR12 rate between treatment arms.

Table 2. *Primary outcome analyses (SVR12)*

Variable				Vitamin D	Placebo
				N=35	N=37
SVR12 (mITT)		Positive (%)		6 (17.1)	10 (27.0)
		Negative (%)		29 (82.9)	27 (73.0)
SVR12* Per protocol		Positive (%)		1 (3.3)	3 (10.0)
		Negative (%)		29 (96.7)	27 (90.0)
Gender		Female (%)		10 (28.6)	13 (35.1)
		Male (%)		25 (71.4)	24 (64.9)
Genotype	1	Total achieving SVR		12	11
			Interferon and ribavirin	*4*	*5*
			Intereferon, ribavirin, telaprevir	*1*	*0*
			Interferon, ribavirin, boceprevir	*1*	*0*
			Interferon, ribavirin, sofosbuvir	*3*	*0*
			Interferon, ribavirin, simeprevir	*3*	*6*
		Total not achieving SVR)		1	1
			Interferon and ribavirin	*1*	*0*
			Interferon, ribavirin, boceprevir	*0*	*1*
		Total genotype 1 for which SVR status unknown		1	2
	3	Total achieving SVR		17	16
			Interferon and ribavirin	*13*	*8*
			Interferon, ribavirin, sofosbuvir	*4*	*8*
		Total not achieving SVR (interferon, ribavirin)		0	2
		Total genotype 3 for which SVR status unknown		4	5

*12 missing SVR12 excluded

Secondary Outcomes

The Proportion of Eligible Patients Undergoing Therapy for HCV Infection Who Drop Out

In those patients consented to participate in the trial as described in the CONSORT diagram above 100 consented and only 72 started therapy. The major reason for this was not fulfilling entry criteria, the second commonest reason was failure to attend further appointments. 12 /72 (17%) consented participants failed to complete the trial. A breakdown of participant recruitment and retention by site is provided in table 3.

Table 3. *Recruitment by site*

Health board	No. randomised	Recruitment per month	Recruitment per 100,000 population	No. with SVR data available (%)
NHS Tayside	15	0.8	3.8	12 (80)
NHS Lothian	7	0.4	0.9	5 (71)
NHS Forth Valley	7	0.4	2.3	7 (100)
NHS Greater Glasgow and Clyde	39	2.2	3.0	33 (85)
NHS Grampian	4	0.2	0.8	3 (75)

The Effect of Supplementation with Vitamin D3 on Adherence to Standard HCV Therapy

The effect of supplementation with Vitamin D3 on adherence to standard HCV therapy was assessed using survival analysis and plotted using Kaplan-Meier plots. The survival analysis of time to drop-off or study completion (adherence) indicated no significant difference between placebo and drug (hazard ratio = 1.3; 95%CI 0.8 to 2.1; p=0.33).

Adverse Events

Adverse events in the trial are listed, broken down by intervention, in Table 4 by standard listing of numbers of each condition. Most events were non-serious and were related to expected side effects from interferon/ribavirin therapy. There was an excess of respiratory infections in the vitamin D arm, this is probably spurious and a reflection of small numbers, as other vitamin D trials have suggested that vitamin D may be protective against respiratory infections[16].

Table 4. *Adverse events*

Category	Vitamin D	Placebo
Blood and lymphatic system disorders	0	4
Ear and labyrinth disorders	0	1
Gastrointestinal disorders	16	21
Immune system disorders	0	1
Worsening Liver function tests	1	2
Metabolic disorders	2	4
Musculoskeletal disorders	2	4
Nervous system disorders	3	7
Psychiatric disorders	13	18
Urinary tract infection	4	0
Other renal/urological disorders	1	0
Reproductive system/breast disorders	2	1
Respiratory tract infection	11	2
Other Respiratory disorders	9	10
Dermatological disorders	18	17
Vascular disorders	2	1
Other Infections (excl respiratory and urinary infections)	2	6
Other	9	8
TOTAL	95	107
Deaths	0	0
Hospitalisations	1	2

Discussion

Key Findings

We performed the first randomised, placebo-controlled parallel group trial to investigate the effects of vitamin D supplementation on response to interferon-based treatment for HCV. We achieved the aim of performing a pilot trial to assess the feasibility of recruitment to this trial design and to estimate the effect size of vitamin D supplementation to allow planning for a larger trial.

We observed no significant difference in SVR between the vitamin D and placebo groups which was not unexpected given the pilot nature of the trial. A trend towards improved SVR in the vitamin D group was observed (83% vs 73%, p= 0.44) and the groups were otherwise matched suggesting that this effect was independent of baseline characteristics.

The effect size had not been rigorously investigated prior to this study however our effect size was less than that seen in previous Israeli studies, which both demonstrated a statistically significant increase in SVR with vitamin D supplementation [13, 14]. This may be related the more rigorous double-blind trial design which we adopted.

Strengths

This trial was conducted in a group of patients known to have difficulty accessing healthcare and with a known high rate of drop-out from care [17]. It was therefore predicted that involving this population in a research study would be challenging. Despite this our study delivered reasonable recruitment and retention in a purely National Health Service (NHS) environment. Ultimately the drop-out rate observed in the study (16.7% dropout post-randomisation) was comparable to standard HCV care drop-out rates and reflects the real world nature and applicability of the study[18, 19].

Limitations

We aimed to recruit 100 participants to the trial and ultimately 72 were enrolled and underwent randomisation. A key limitation to recruitment was the rapidly evolving therapeutic landscape with multiple new interferon-free treatments being approved and individual preference for these less toxic regimens. Extending the study to enable further recruitment was not appropriate given the increased efficacy and reduced toxicity of these novel antivirals. We initially intended to assess for differences between individuals who declined trial involvement and those who consented. However, this was confounded by the adoption of interferon-free regimens during the study period and therefore these data has not been presented as they are no longer meaningful.

The use of interferon add-on therapies increased as the trial progressed and therefore multiple participants in both arms of the study received either telaprevir, boceprevir, sofosbuvir or simeprevir. Use of these agents complicates interpretation of our results, however it would have been unethical to withhold these from study participants given the dramatically increased SVR associated with these new agents. Equally the trend towards vitamin D supplementation improving SVR is of greater interest given the higher use of novel more effective antivirals in the placebo arm of our study.

60 of the 72 (83%) participants ultimately attended for post-treatment viral PCR to assess for SVR. It is therefore unknown if the treatment was effective in the other 12 individuals. It is common in HCV therapy for 5-10% of patients to drop out of therapy for patient related reasons, for a further 5% to have therapy stopped for safety side effects and for a further 5% to have therapy stopped due to lack of efficacy. Such patients are very difficult to keep in follow up to collect SVR data when the patient believes the therapy has not worked. Our observed dropout rate (17%) is therefore in keeping with real world published data[18, 19].

The quality of our data was also affected by a population of participants with variable attendance rates and chaotic lifestyles. Study visits often did not take place when planned and not all study procedures could be conducted at times planned in the protocol. In addition, all study activities were performed by NHS staff and not trained research assistants; an approach that reflected the pragmatic nature of the trial design and the realities of delivering a clinical service to a complex group of patients.

Generalisability

This pilot study was not designed to provide generalizable conclusions on the efficacy of the addition of vitamin D to interferon and ribavirin-

based HCV treatment. Our result does not warrant a change in clinical practice but helps to inform a future larger trial.

Interpretation

Today the Scottish Medicines Consortium (SMC) has approved all-oral pan-genotypic regimens for HCV with SVR of over 97%[20] Given this it is not surprising that it became increasingly challenging to recruit patients to a study and treatment which was rapidly becoming obsolete. However, it should be noted that the novel direct-acting antivirals are extremely expensive and funding will be a challenge in even the most highly-funded healthcare systems. The largest burden of HCV continues to be felt in lower and middle income countries (LMICs) and in these nations interferon and ribavirin are likely to be of continued importance for some years. An economical means to augment response to this regimen may, therefore, still provide meaningful benefit to both patients and to healthcare systems in LMICs.

Given the widespread adoption of direct-acting antivirals it is unlikely that a future large trial of vitamin D vs. placebo as an adjunct to interferon/ribavirin therapy will be conducted in any high-income country. In addition, using vitamin D as an adjunct to these novel therapies is not required given the near 100% response rates. However, such a trial could be performed in LMICs, could still be informative and could lead to a change in practice.

Based upon our data such a trial would require 540 participants (270 per group) to detect a similar difference in effect with 80% power, assuming alpha=0.05. A larger number of participants would initially be required given the anticipated drop-out rates. Our trial enrolled 72 participants for which 60 (83%) have available SVR data. This 17% drop-out rate is comparable to that seen in other HCV treatment studies. Given this, if SVR data were to be obtained for 540 participants an initial enrolment and randomisation of 650 individuals would be required.

It is difficult to draw valid conclusions regarding recruitment given the previously discussed difficulties which we encountered. In total across the 5 Scottish health boards we recruited 4 individuals per month during the 18 month trial period. A predicted158 month (13 year) recruitment period to enrol 632 participants from a majority of the Scottish population in a larger study is unachievable. However if this were performed in a lower/middle-income country recruitment would be less affected by the widespread availability of interferon-free regimens.

The exact treatment regimen to be utilised in any future interferon/ribavirin study involving vitamin D vs. placebo is unclear and would be dependent upon the availability and cost of add-on direct acting antivirals which would boost overall efficacy.

In addition, recent evidence suggests that the monthly vitamin D bolus utilised in our study might be less effective than daily or weekly dosing and therefore a future trial would likely opt for more frequent dosing[16].

Conclusion

Our study adds further credence to the hypothesis that vitamin D plays a crucial role in modulating the immune response to infection and inflammation. Whilst novel therapeutics have now replaced interferon/ribavirin regimens in high-income nations, interferon/ribavirin may continue to be an important therapeutic option in LMICs. Current evidence is insufficient to recommend adding vitamin D to interferon/ribavirin regimens, but our results support the case for larger trials of vitamin D supplementation as adjunctive therapy in patients with HCV treated with interferon/ribavirin. Such trials should be conducted in populations likely to be treated in this way – i.e. patients in LMICs.

List of Abbreviations

25OHD – 25-hydroxyvitamin D

HCV – hepatitis C virus

LMIC – lower and middle income countries

NHS – National Health Service

PCR – polymerase chain reaction

SMC – Scottish Medicines Consortium

SVR – sustained virologic response

Declarations

Ethics Approval

The trial was approved by East of Scotland Research Ethics committee (approval number 138656), and Clinical Trials Authorisation was given by MHRA (EudraCT number 2013-003573-10) and ISRCTN number NCT 02053519.

Written consent was provided by all participants prior to enrolment in the trial.

Availability of Data and Materials

Raw data are available for collaborative, non-profit use on request from the authors.

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