



Clinical trial results:

Can Vitamin D supplementation improve Hepatitis C cure rates: A pilot multicentre randomised controlled clinical trial

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2013-003573-10 |
| Trial protocol | GB |
| Global end of trial date | 22 December 2015 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 13 May 2017 |
| First version publication date | 13 May 2017 |
| Summary attachment (see zip file) | Summary results viaduct (ct_result_2013-003573-10 Viaduct Dillon.pdf) |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 2012GA03 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|------------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02053519 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Sponsor R&D number: 2012GA03 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | University of Dundee |
| Sponsor organisation address | Ninewells Hospital, Dundee, United Kingdom, DD1 9SY |
| Public contact | Prof John Dillon, University of Dundee, 44 01382383017, j.f.dillon@dundee.ac.uk |
| Scientific contact | Prof John Dillon, University of Dundee, 44 01382383017, j.f.dillon@dundee.ac.uk |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 05 December 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 22 December 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 December 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to test if vitamin D supplementation improves the chances of standard treatment for HCV infection being effective. To test this we will measure if there is an improvement in the virologic response - ie the level of virus in the blood, 12 weeks after completion of treatment.

Protection of trial subjects:

Trial exclusion criteria were designed to minimize the risk of hypercalcemia or renal stones (known side effects of vitamin D therapy); drug exclusions were designed to minimize the risk of interactions with vitamin D.

Adverse events were sought at each clinic visit; the directly observed nature of the vitamin D administration once a month ensured close observation of participants throughout the trial.

Background therapy:

Standard HCV therapy was commenced 1-4 weeks after the first dose of vitamin D or placebo. Standard treatment for HCV is generally for 24 weeks. Some genotype 1 patients who do not respond to therapy at week 4 or 12 will have all anti-viral therapy stopped. Other genotype 1 patients who respond but do not become virus negative by 12 weeks of therapy will continue on a further 24 week course of standard therapy, total duration 48 weeks. Standard therapy for HCV genotype 1 patients changed as the trial commenced and some patients received sofosbuvir in addition to interferon for 12 weeks.

Evidence for comparator:

Placebo was selected (in addition to standard therapy) as the aim of the trial was to test efficacy of vitamin D in addition to standard therapy, rather than instead of standard therapy.

| | |
|---|------------------|
| Actual start date of recruitment | 01 November 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 72 |
| Worldwide total number of subjects | 72 |
| EEA total number of subjects | 72 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|----|
| wk | |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 72 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from hepatitis C treatment services across multiple Scottish secondary care sites

Pre-assignment

Screening details:

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

Period 1

| | |
|------------------------------|---|
| Period 1 title | Randomised treatment (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

Matching IMP and placebo (base oil) were prepared by an independent provider (Tayside Pharmaceuticals) who dispensed identical bottles with no external indication of allocation group

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Vitamin D3 |

Arm description:

Oral vitamin D3 100,000 units once per month

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Cholecalciferol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

100,000 units once a month, given as 5mls of 20,000 units/ml product (Vigantol oil)

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Matching placebo given once a month

| | |
|--|---------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

5mls of matching placebo (Mygliol oil as used as base oil in Vigantol oil preparation) given once a month

| Number of subjects in period 1 | Vitamin D3 | Placebo |
|---------------------------------------|------------|---------|
| Started | 35 | 37 |
| Completed | 30 | 30 |
| Not completed | 5 | 7 |
| Lost to follow-up | 5 | 7 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Vitamin D3 |
|-----------------------|------------|

Reporting group description:

Oral vitamin D3 100,000 units once per month

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Matching placebo given once a month

| Reporting group values | Vitamin D3 | Placebo | Total |
|---|------------|---------|-------|
| Number of subjects | 35 | 37 | 72 |
| Age categorical Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 0 |
| Newborns (0-27 days) | | | 0 |
| Infants and toddlers (28 days-23 months) | | | 0 |
| Children (2-11 years) | | | 0 |
| Adolescents (12-17 years) | | | 0 |
| Adults (18-64 years) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 42.5 | 41.7 | |
| standard deviation | ± 11.6 | ± 8.7 | - |
| Gender categorical Units: Subjects | | | |
| Female | 10 | 13 | 23 |
| Male | 25 | 24 | 49 |

End points

End points reporting groups

| | |
|--|-----------------------------|
| Reporting group title | Vitamin D3 |
| Reporting group description: Oral vitamin D3 100,000 units once per month | |
| Reporting group title | Placebo |
| Reporting group description: Matching placebo given once a month | |
| Subject analysis set title | ITT analysis set |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: All participants with a value for the primary outcome (SVR12) | |

Primary: SVR12 (sustained virologic response at 12 weeks)

| | |
|--|--|
| End point title | SVR12 (sustained virologic response at 12 weeks) |
| End point description: Sustained virologic response 12 weeks after stopping treatment. Response = undetectable Hep C RNA at any point beyond 12 weeks post end of interferon-based treatment. Missing data analysed as treatment failure. | |
| End point type | Primary |
| End point timeframe: 12 weeks after cessation of standard (interferon based) Hep C treatment | |

| End point values | Vitamin D3 | Placebo | ITT analysis set | |
|-----------------------------|-----------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 35 | 37 | 72 | |
| Units: patients | | | | |
| Treatment success | 29 | 27 | 56 | |
| Treatment failure | 6 | 10 | 16 | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Adjusted odds ratio for treatment success |
| Comparison groups | Vitamin D3 v Placebo |
| Number of subjects included in analysis | 72 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.44 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.74 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.43 |
| upper limit | 6.97 |

Secondary: Time to stopping standard treatment (adherence)

| | |
|---|---|
| End point title | Time to stopping standard treatment (adherence) |
| End point description: Time to stopping standard (interferon-based) treatment as a measure of adherence; comparison between vitamin D and placebo groups | |
| End point type | Secondary |
| End point timeframe: Baseline to 48 weeks | |

| End point values | Vitamin D3 | Placebo | | |
|---------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 | 37 | | |
| Units: days | | | | |
| median (inter-quartile range (Q1-Q3)) | 195 (112 to 270) | 224 (119 to 303) | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Hazard ratio-time to stopping standard treatment |
| Statistical analysis description: Cox regression analysis | |
| Comparison groups | Placebo v Vitamin D3 |
| Number of subjects included in analysis | 72 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.33 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.78 |
| upper limit | 2.09 |

Secondary: 25-hydroxyvitamin D levels

| | |
|-----------------|----------------------------|
| End point title | 25-hydroxyvitamin D levels |
|-----------------|----------------------------|

End point description:

Change from baseline averaged over follow up period

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to 48 weeks

| End point values | Vitamin D3 | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 | 37 | | |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | 16.7 (± 39.5) | -7.9 (± 21.8) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Between group difference in 25OHD levels |
| Comparison groups | Vitamin D3 v Placebo |
| Number of subjects included in analysis | 72 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (net) |
| Point estimate | 24.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 12.2 |
| upper limit | 37.2 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening visit to 48 weeks (final visit)

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 18 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Vitamin D3 |
|-----------------------|------------|

Reporting group description: -

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo

| Serious adverse events | Vitamin D3 | Placebo | |
|---|---|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 2 / 37 (5.41%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Skin ulcer | Additional description: Ulcer on leg | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Intentional overdose | Additional description: Intentional heroin overdose | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Vitamin D3 | Placebo | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 28 / 35 (80.00%) | 31 / 37 (83.78%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 6 / 37 (16.22%) | |
| occurrences (all) | 1 | 6 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 6 / 35 (17.14%) | 8 / 37 (21.62%) | |
| occurrences (all) | 6 | 9 | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 3 / 37 (8.11%) | |
| occurrences (all) | 3 | 4 | |
| Appetite disorder | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 3 / 37 (8.11%) | |
| occurrences (all) | 2 | 3 | |
| Throat irritation | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 2 / 37 (5.41%) | |
| occurrences (all) | 3 | 2 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 3 / 37 (8.11%) | |
| occurrences (all) | 3 | 3 | |
| Influenza-like illness | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 2 / 37 (5.41%) | |
| occurrences (all) | 2 | 2 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 1 / 37 (2.70%) | |
| occurrences (all) | 8 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 7 / 37 (18.92%) | |
| occurrences (all) | 5 | 7 | |

| | | | |
|------------------------------------|-----------------|-----------------|--|
| Pruritis | | | |
| subjects affected / exposed | 5 / 35 (14.29%) | 3 / 37 (8.11%) | |
| occurrences (all) | 5 | 3 | |
| Rash | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 2 / 37 (5.41%) | |
| occurrences (all) | 5 | 2 | |
| Psychiatric disorders | | | |
| Depressed mood | | | |
| subjects affected / exposed | 6 / 35 (17.14%) | 6 / 37 (16.22%) | |
| occurrences (all) | 6 | 6 | |
| Renal and urinary disorders | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 37 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Metabolism and nutrition disorders | | | |
| Weight decreased | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 0 / 37 (0.00%) | |
| occurrences (all) | 4 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 31 October 2013 | Revision of protocol to v2.0 with additional exclusion criteria added |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Recruited fewer participants than originally powered for. Changes in background therapy for hepatitis C mean results may not now be applicable to current standard of care. High cure rates in placebo group limit ability to detect treatment effect.

Notes: