Evaluation of efficacy of a nanoparticle based vitamin D formulation in correction of vitamin D levels in patients with documented deficiency or insufficiency of vitamin D

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ABSTRACT

Background: In India more than 90% of apparently healthy Indians have subnormal 25(OH) D levels. To maintain sufficient vitamin D level, apart from sunlight and food containing vitamin D, supplementation with vitamin D is also required. The objective of this study was to find out effectiveness of nanoparticle based vitamin D formulations in patient of vitamin D deficiency and insufficiency.

Methods: This was a prospective, open label, single arm, non-comparative, dose response post-marketing efficacy study (PMS) – phase-4 study to find the effectiveness of a nanoparticle based vitamin D formulation in adult patients between 18 to 65 years of either gender, attending/visiting the study site with documented deficiency or insufficiency of vitamin D. Each subject planned to receive 60,000 IU of nanoparticle based vitamin D, once weekly, for 8 weeks orally. Serum 25(OH) D levels were measured at baseline, 4 and 8 week.

Results: The mean baseline serum 25(OH) D levels were 15.90. After treatment with nanoparticle based vitamin D there was a significant increase in the serum vitamin D levels at 4 weeks (41.03) and 8 weeks (31.38) (p<0.0001). Patients who have received treatment for at least 4 weeks' period (n=38), the improvement (serum 25(OH) D >30 ng/ml) was seen in 84.2% patients (n=32) at the end of 4 weeks itself. There is significant increased (<0.0001) in the physical component scores of the SF-12 QOL questionnaire after 8 weeks of therapy.

Conclusions: Nanoparticle based formulation of vitamin D is effective and safe in correction of vitamin D levels in patients with documented deficiency or insufficiency of vitamin D. Also the safety and tolerability is well accepted and reported good to excellent by patients and physician.

Keywords: Vitamin D, Nanoparticle, 25 (OH) D, Vitamin D deficiency

INTRODUCTION

Vitamin D deficiency has been proposed to contribute to the development of various diseases.1 It has been estimated that one billion people worldwide have Vitamin D deficiency.2 In India more than 90% of apparently healthy Indians have subnormal 25(OH) D levels.3-6 The endocrine society suggests that serum levels of 25 [OH] D less than 20 ng/ml as deficiency and levels between 21-29 ng/mL as insufficiency, while levels of 25[OH] D above 30 ng/mL are optimum levels of the vitamin.7

Sunlight is known to be the primary source of vitamin D and its production in the skin depends on exposure to sunshine, latitude, skin-covering clothes, the use of sunscreen lotions and skin pigmentation in healthy individuals. The status of vitamin D depends on the...
production of vitamin D3 and vitamin D intake through the diet or vitamin D supplements.\(^8\) Other than low dietary vitamin D intake and poor exposure to sunlight there are several factors causing Vitamin D deficiency like, increased pollution, repeated unplanned and unspaced pregnancies with dietary deficiency.\(^9,11\)

Very few foods naturally contain vitamin D, and foods that are fortified with vitamin D are often inadequate to satisfy either a child’s or an adult’s vitamin D requirement.\(^12\) In India current recommendations for correction of vitamin D level, is by giving 60,000 IU of oral Vitamin D on a weekly basis for 8 weeks.\(^6,13\) There is a clear linear relationship between oral vitamin D intake and the resulting serum 25-hydroxyvitamin D (25 (OH) D) concentration, as the hydroxylation of vitamin D intake is not regulated tightly.\(^14\) The serum 25(OH)D response to oral supplementation is positively related to the dose given but inversely related to initial serum 25 (OH) D concentration.\(^15,16\) Vitamin D deficiency patients present with generally musculoskeletal symptoms, such as bone pain, myalgias, and generalized weakness.\(^17\)

A published literature suggests that vitamin D3 granules eight weeks of vitamin D3 60,000 IU/week oral granules supplementation increased serum 25 (OH) D to optimal levels in most of the subjects with Vitamin D deficiency.\(^8\) It has been reported that approximately 50% of orally ingested vitamin D3 is absorbed.\(^10\) In vitro study done on rat intestine showed that average absorption of Nano particle based vitamin D was 77.83±0.24%. The predicted human absorption may be more than 90%. This study also showed that nano particle based vitamin D absorbed through various part of rat small intestine like duodenum, jejunum, and ileum.\(^19\) Until today no study on nano particle based vitamin D formulation in patients of vitamin D deficiencies is performed. Hence, this study was planned to evaluate the efficacy of nanoparticle based vitamin D formulation in correcting the vitamin D levels after a weekly therapy for 8 weeks.

**METHODS**

This was a prospective, open label, Single arm, non-comparative, dose response post-marketing efficacy study (PMS) – phase-4 study of a nanoparticle based vitamin D formulation in patients with vitamin D deficiency or insufficiency. The study was conducted for around 5 months (24 June 2016 to 1\(^{st}\) December 2016). This was an investigator initiated study at one centre. Primary objective was to evaluate efficacy of a nanoparticle based vitamin D formulation for correcting the vitamin D levels in patients of vitamin D deficiency or insufficiency after a weekly therapy for 8 weeks. Along with this, as a part of secondary objective, patient profile of vitamin D deficient or insufficient patients were assessed. Improvement in quality of life (QOL) of study subjects was evaluated through assessments at baseline and end of 8 weeks. The response to a nanoparticle based vitamin D at the end of therapy was evaluated using patient and physician assessment.

Adult patients between 18 to 65 years of either gender, attending/visiting the study site with documented deficiency or insufficiency of vitamin D (<30 ng/ml) or sign and symptoms of deficiency or insufficiency of vitamin D were screened for enrolment in the study. Patients with uncontrolled hypertension and diabetes mellitus, history of malabsorption, kidney stones, hypoparathyroidism, or growth hormone deficiency, known hypersensitivity to vitamin D supplements and patients on medications interfering with vitamin D metabolism were excluded. Patients who fulfilled these criteria were enrolled in the study after obtaining informed consent.

Each subject planned to receive 60,000 IU of nano particle based vitamin D, once weekly, for 8 weeks orally. Total study duration was of 8 weeks, with visit at baseline, week 4 and week 8. All patients underwent details physical examination and also different laboratory investigations were performed. Serum 25-OH vitamin D assessed at all three visits. At the end of study patients were also assessed for: Patients global assessment of efficacy, patients global assessment of tolerability to therapy, physician global assessment of efficacy based on symptoms, physician global assessment of efficacy based on improvement in vitamin-D levels, physician global assessment of tolerability to therapy. Quality of life questionnaire (SF-12 health survey form) assessed at baseline and at the end of study.

**Statistical methods**

Sample size was based on statistical calculations. In a paired t-test comparing 25 (OH) D, with assuming pre- and post-mean and standard deviation of 27±15 and 34±10 with significance level of 5% and null difference 0, a sample size of 35 was required to obtain a power of at least 90% to detect a assumed mean difference of 7 from pre to post visit. Considering ~30% dropouts/withdrawals, 47 subjects were required for single arm observation studies.

Continuous variables are summarized with the descriptive statistics \( n \) (number of observations), mean, standard deviation, median, minimum and maximum values as appropriate. A summary of categorical data was done through numbers and percentages. If the data was not available, missing category is presented.

Full analysis set (FAS): This analysis set is as close as possible to the intention-to-treat (ITT) data set which includes all subjects screened and enrolled. The subjects should have taken at least one dose of study medication. All safety and tolerability analysis was done on the FAS. Per-protocol set (PPS): All patients who satisfied the study criteria and completed the study as per the study.
protocol are considered as PPS population. All efficacy analysis was done on the PPS.

Paired t-test statistical analysis was performed to assess the statistical significance of the difference between the baseline and follow-up visits, for each evaluable parameter. A p value <0.05 was considered statistically significant.

Ethical conduct of the study

The study was carried out in compliance with the study protocol, and in accordance with the principles of the Declaration of Helsinki, ICH-GCP, applicable local regulatory requirements and the site standard operating procedures (SOPs).

The documents were reviewed and approved by the Ethical Committee of the Suraksha Ethics Committee.

RESULTS

A total of 43 patients enrolled in this study; of which 38 patients were included in PPS dataset and all 43 patients included in FAS data set. Thirteen (13) were male and 30 were female enrolled, and of which majority of the patients (51.2%) were between 31 to 40 years of age (22/43), whereas 20.9% of the patients were above 50 years of age (9/43) and 18.6% were between 41 to 50 years of age (8/43).

Out of 43 patients who were vitamin D deficient, 6 were obese (13.96%), 22 were overweight (51.16%) and 15 were normal (34.88%).

Vitamin D deficiency (serum 25 [OH] D <20 ng/ml) was observed in 31 (72.09%) patients, whereas insufficiency (serum 25 [OH] D 20 to 30 ng/ml) was observed in 12 (27.91%) patients enrolled. Majority of vitamin D deficient patients include service/salaried 17/31 (54.8%) and housewives 12/31 (38.7%) which is then followed by patients who have business or are retired. Similar pattern was seen in vitamin D insufficiency patients service/salaried 6/12 (50%) and housewives 4/12 (33.3%).

Of the 43 patients, 28 patients (65.1%) had no exposure to the sunlight, 9 patients (20.9%) had less than 30 minutes of sunlight exposure per day, and 6 patients (14.0%) had more than 30 minutes of sunlight exposure per day.

At baseline, there were no systemic abnormalities reported by the patients. Only one female patient had white PV discharge (gynaecological problem). All patients reported symptoms suggestive of vitamin D deficiency. The non-specific symptoms include generalized body pain or isolated pain, muscle or bone pain, generalized weakness, muscular weakness, difficulty in standing, squatting, walking and frequent falls. Other specific symptoms include shoulder pain, heel pain, backache, knee pain, elbow pain, joint pain, calf pain and hand and leg pain.

There was significant (p <0.0001) increase in the serum vitamin D levels from baseline (15.90 ng/ml) to 4 weeks (41.03 ng/ml) and 8 weeks (31.38 ng/ml) of therapy with nanoparticle vitamin D. The detailed results are given in Table 1 and Figure 1.

Table 1: Serum 25[OH] D (ng/ml) at baseline, week 4 and week 8 (PPS).

| Sr. 25[OH]D | N  | Mean  | Std. deviation |
|-------------|----|-------|----------------|
| Baseline    | 38 | 15.9  | 6.45           |
| 4 weeks     | 38 | 41.03 | 13.06          |
| 8 weeks     | 38 | 31.38 | 10.62          |

% change from baseline

| Change from baseline | N  | Mean  | Std. deviation |
|----------------------|----|-------|----------------|
| 4 weeks              | 38 | 25.12 | 11.68          |
| 8 weeks              | 38 | 15.48 | 11.37          |

| % change from baseline | N  | Mean  | Std. deviation |
|------------------------|----|-------|----------------|
| 4 weeks                | 38 | 202.47| 161.51         |
| 8 weeks                | 38 | 140.87| 148.6          |

Figure 1: Mean serum 25 [OH] D (ng/ml) at baseline, week 4 and week 8 (PPS).

Patients who have received vitamin D$_3$ therapy for at least 4 weeks period, the improvement (serum 25 [OH] D >30 ng/ml) was seen in 84.2% (n=32) patients at the end of 4 weeks itself and 39.5% (n=15) patients at the end of 8 weeks. Out of these 32 patients, 31 patients achieved very high serum 25 (OH) D level at 4 weeks, so to avoid toxic level of 25 (OH) D in these patient, therapy was discontinued after 4 week. Amongst patients who received only 4 weeks of therapy (n=31), 41.9% (n=13) of patients maintain normal 25 (OH) D level at 8 weeks and this improvement is similar in those with deficiency and insufficiency. Amongst patients (n=7) who received complete 8 weeks of therapy, 16.7% (n=1) and 33.3% (n=2) of patients achieved normal serum 25 (OH) D level at the end of 4 and 8 week respectively. The detailed results are given in Table 2.
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cates the effectiveness of

vitamin D deficiency and insufficiency patients.

This was an investigator initiated post marketing study to

DISCUSSION

for all patients (100.0%) by the physician
tolerability to therapy was reported as excellent

A total of three (7.0%) patients reported four (9.3%)
adverse events of which one

50.0% in patients with age <50 y

patients over 50 years of age (75.0% versus less than

Improvement in MCS scores was similar in males and

50.0% in patients with age <50 y

Physical health component (PCS) scores observed in 86.8% patients after 8

week of therapy.

The improvement in quality of life (QOL) from

The improvement in the quality of life (QOL) from

baseline to end of therapy using 12 item Short form

survey (SF-12) form is reported as number and

percentage of patients showing improvement. There is

significant increased (<0.0001) in the physical

component scores observed in 86.8% patients after 8

week of therapy. Improvements in PCS scores were

similar in males and females, different BMI categories,

age groups. Improvement in the mental component scores

after 8 weeks was observed in 52.6% patients.

Improvement in MCS scores was similar in males and

females and those with different BMI categories.

However, the improvement in MCS scores were better in

patients over 50 years of age (75.0% versus less than

50.0% in patients with age <50 years.)

A total of three (7.0%) patients reported four (9.3%)
adverse events of which one event was considered serious

(SAE) due to hospitalisation. This event was recovered

and was not related to the study medication.

The global tolerability to therapy was reported as

excellent to good by 97.5% patients. The global

tolerability to therapy was reported as excellent to good

for all patients (100.0%) by the physician.

DISCUSSION

This was an investigator initiated post marketing study to

assess the efficacy of nano particle based vitamin D in 43

vitamin D deficiency and insufficiency patients.

There were no differences in the duration of therapy in

different BMI categories, age groups and sunlight

exposure.

Excellent to good response was reported by physician as

an assessment of efficacy of therapy based on symptoms

of vitamin D deficiency in 84.2% patients at the end of

therapy. Marked to good improvement was reported by

physician as an assessment of efficacy of therapy based

on 25 OH (D) level in 36.8% patients at the end of

therapy.

Nanotechnology (nanoparticles) may help in improving

the oral bioavailability of nutrients that have poor water

solubility. The improvement in absorption could be

because nanoparticles reduce the necessity of lipids in the

absorption, provide protection against harsh environment

of the gastrointestinal tract and possibly enhance trans-

mucosal transport. Other researchers have also

suggested that nanoparticles of vitamin D 3 may also

enhance important properties of vitamin D supplements,

like therapeutic efficacy, photo-stability and bio-
degradation.

Higher body fat percentage or higher BMI have been

associated with smaller increases in 25 (OH) D levels in response to vitamin D supplementation. Also the change in 25 (OH) D concentration was significantly inversely associated with BMI, central body fat, weight and waist circumference. In this study there were no difference observed in the duration of therapy in different BMI categories. In this study, majority of the patients were between 31 to 40 years of age followed by were above 50 years of age. Aging has frequently been reported to be associated with lower levels of 25 (OH) D in circulation. It has been proposed that the capacity of the epidermis to synthesize vitamin D (due to a decrease in the precursor 7-dehydrocholesterol) and the expression of vitamin D binding protein is compromised by aging. However in this study there were no differences in the duration of therapy in different age groups. In this study, vitamin D deficiency was higher in females. Song et al also reported

Table 2: Percentage of patients with serum 25 [OH] D >30 ng/ml baseline, week 4 and week 8 (PPS).

|                      | 4 weeks N | 4 weeks No. | 4 weeks Percent | 8 weeks N | 8 weeks No. | 8 weeks Percent |
|----------------------|-----------|-------------|----------------|-----------|-------------|----------------|
| All patients (at least 4 weeks) | 38        | 32          | 84.2           | 15        | 11          | 39.3           |
| - Patients with deficiency | 28        | 23          | 82.1           | 11        | 9           | 39.3           |
| - Patients with insufficiency | 10        | 9           | 90.0           | 04        | 0           | 40.0           |
| Only 4 wks. Nano particle vitamin D₃ therapy | 31 | 31 | 100.0 | 13 | 41.9 |
| - Patients with deficiency | 22        | 22          | 100.0          | 09        | 0           | 40.9           |
| - Patients with insufficiency | 09        | 9           | 100.0          | 04        | 0           | 44.4           |
| Only 8 wks. Nano particle vitamin D₃ therapy | 07 | 01 | 16.7 | 02 | 33.3 |
| - Patients with deficiency | 06        | 0           | 14.3           | 02        | 0           | 28.6           |
| - Patients with insufficiency | 01        | 0           | -              | 00        | 0           | -              |
that vitamin D deficiency is higher in women than in men in all age groups. The sex differences in the prevalence of vitamin D deficiency could be explained by a lack of exposure to sunlight such as more frequent sun protection in women. An interviewer survey of 547 middle-aged and elderly Chinese women reported that many women (62.3%) actively avoid sunlight exposure by staying indoors and using sunscreen products and parasols.

This study shows that tolerability with nano particle based vitamin D therapy was good. Another study done on Nano particle based formulation of vitamin D3 in Indian prescriber concluded that most of the doctors confirmed that nanotechnology can improve oral absorption of vitamin-D, and over one-third doctors recommended the use of nanoformulation for all patients with vitamin D deficiency. In terms of the efficacy, tolerability and patient convenience, nanoparticle formulation was the preferred formulation by most of the doctors over other conventional formulations. The nanoformulation was also reported to be convenient and widely accepted by the patients as well. In conclusion, the study results reflect that Nano particle based vitamin D formulation would be beneficial for patients with vitamin D deficiency.

In this study, Nano particle based formulation of vitamin D3 is effective and safe in correction of vitamin D levels in patients with documented deficiency or insufficiency of vitamin D. Also the safety and tolerability is well accepted and reported good to excellent by patients and physician. Also, this study showed that QOL improves with the use of Nano particle based formulation of vitamin D3 for the correction of vitamin D deficiency.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Ethical Committee of the Suraksha Ethics Committee

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