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Safety and efficacy of Vitamin D_3 supplementation with Imatinib in Chronic Phase- Chronic Myeloid Leukaemia: an Exploratory Randomized Controlled Trial

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ABSTRACT

Objectives The study aimed to compare early molecular response (EMR) rates at 3 months of imatinib therapy with and without vitamin D_3 supplementation in patients newly diagnosed with chronic-phase chronic myeloid leukaemia (CML-CP). The secondary objective was to assess the effects of vitamin D_3 on complete haematological response (CHR) and its safety.

Design Double-blind, placebo-controlled, exploratory randomised trial.

Setting Tertiary care hospital in northern India.

Participants Treatment-naive patients with chronic phase chronic myeloid leukaemia (n=62) aged >12 years were recruited from January 2020 to January 2021. Patients with progressive disease, pregnancy and hypercalcaemia were excluded.

Intervention Oral vitamin D_3 supplementation (60 000 IU) or matched placebo was given once weekly for an initial 8 weeks along with imatinib after randomisation with 1:1 allocation ratio.

Primary and secondary outcome measures The primary outcome was to compare EMR (defined as *BCR-ABL1* transcript level ≤10%, international scale) at 3 months. The secondary outcomes were to compare effect of the intervention on CHR, correlation of 25(OH)$2D_3$ levels with treatment response and safety according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.

Results At baseline, 14.5% of the patients had normal vitamin D_3 levels. EMR at 3 months was attained in 24 patients (82.7%) of the vitamin D_3 group and 21 (75%) of the placebo group (OR 1.6, 95% CI 0.37 to 7.37, p=0.4). A significant difference in vitamin D_3 levels from baseline to the end of study was observed. Patients with vitamin D_3 supplementation did not achieve higher CHR in comparison with placebo (OR 1.3, 95% CI 0.25 to 7.23, p=1.0). Vitamin D3 levels were not significantly correlated with *BCR-ABL1* levels. No dose-limiting toxicities were observed.

Conclusion Vitamin D_3 levels were low among patients with CML-CP in this study. Vitamin D_3 supplementation with imatinib therapy did not have significant effect on EMR or CHR. Further clinical trials could be undertaken to assess the effective dosage and duration of vitamin D_3 supplementation in these patients.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A single-centre, randomised, double-blind, parallel-group, placebo-controlled trial was designed in accordance with the trial objectives.
⇒ Treatment-naive patients with chronic phase-chronic myeloid leukaemia were randomised to receive vitamin D_3 supplementation as an add-on therapy with imatinib.
⇒ The study duration was limited to 3 months; long-term outcomes such as major molecular response could not be evaluated.

Trial registration number CTRI/2019/09/021164.

INTRODUCTION

Chronic myeloid leukaemia (CML) is a myeloproliferative disorder arising from the haematopoietic stem cell compartment.[1] Clinical presentation may widely range from incidental findings in laboratory investigations to splenomegaly, abdominal pain, early satiety, fatigue, and symptoms of anaemia and bleeding due to platelet dysfunction.[2]

A suspected case of chronic phase- chronic myeloid leukaemia (CML-CP) is diagnosed from complete blood count (CBC) with peripheral smear, bone marrow aspiration biopsy, and cytogenetics and reverse transcriptase quantitative PCR for *BCR-ABL1* transcripts. *BCR-ABL1* is an important predictor of treatment outcome in CML. Transcript levels ≤10% at 3 months are associated with improved long-term outcomes (event-free and overall survival).[3]

The prognosis of CML-CP has drastically improved with the introduction of tyrosine kinase inhibitors (TKIs). Imatinib, a commonly used first-line TKI, has adverse

effect on calcium and phosphorus metabolism. It is also found to decrease calcidiol and calcitriol production by 50% in human keratinocytes.[4 5]

Vitamin D_3 is a fat-soluble vitamin. After exposure to ultraviolet radiation, the skin produces pre-D_3 (cholecalciferol), which is activated after undergoing two hydroxylation processes, the first of which occurs in the liver and results in 25(OH)D3 (calcidiol). The kidney's CYP27B1 enzyme performs the second hydroxylation, which produces 1,25(OH)2D_3 (calcitriol), the main active form of vitamin D_3.[6]

Vitamin D_3 acts as an immunomodulator.[7] The active form of vitamin D, 1,25-dihydroxy vitamin D_3, is present in various extrarenal sites, including cancer cells. Vitamin D_3 exerts its actions on the cell by regulating transcription and indirectly by genomic regulation of cell signalling pathways. The transcription regulatory properties of vitamin D_3 have a wide variety of effects, including antiproliferation, induction of apoptosis, stimulation of differentiation, reduced inflammation, inhibition of invasion, metastasis and angiogenesis.[8]

Human research on therapeutic potential of vitamin D_3 as an add-on therapy in haematological malignancies is sparse. Moreover, vitamin D_3 supplementation can antagonise the adverse effects of imatinib therapy. With evidence from literature that vitamin D_3 has a protective role in cancers, this exploratory randomised controlled trial was planned to assess the role of vitamin D_3 supplementation in patients with CML-CP on imatinib therapy.

Objectives

The primary objective was to compare the early molecular response (EMR) rates (defined as *BCR-ABL1* transcript level ≤10%, international scale (IS)) at 3 months of imatinib therapy with and without vitamin D_3 supplementation in newly diagnosed CML-CP patients.

The secondary objectives were to assess the effect of vitamin D_3 supplementation on complete haematological response (CHR), to explore the safety of vitamin D_3 supplementation and to correlate the baseline vitamin D_3 levels with CML prognostic scores and treatment response in newly diagnosed CML-CP patients.

METHODS

Trial design

The present study was a single-centre, randomised, parallel-group, placebo-controlled, double-blind clinical trial of vitamin D_3 supplementation along with imatinib in patients with CML-CP.

Study setting

The study was conducted by the Department of Pharmacology in collaboration with the Department of Medical Oncology Haematology at All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India. The study was conducted over a period of 12 months, that is, from January 2020 to January 2021. After enrolment, follow-up was done for 12 weeks.

Inclusion criteria

All treatment-naive CML-CP patients aged >12 years and willing to provide written informed consent were included.

Exclusion criteria

Patients in de novo accelerated-phase or blast-phase CML, already started on any other TKI treatment prior to randomisation, pregnant and lactating women, baseline serum calcium >10.5 mg/dL, baseline serum creatinine >2 mg/dL, known history of renal calculi or any known renal complication, and those who were unable to comprehend the interview questions were excluded.

Trial intervention

All patients included in the trial were started with routine management, that is, imatinib 400 mg once daily, after randomisation. Eight sachets of either vitamin D_3 (cholecalciferol, 60 000 IU) or matched placebo sachets (oral rehydration solution, 5 g) were provided to the patients in opaque sealed envelope. They were advised to take the medications once a week orally after lunch with plain water. Based on the laboratory parameters, non-responders to therapy in either the interventional or placebo group were given appropriate treatment as per standard treatment guidelines in the institute. Vitamin D_3 was analysed by automated immunoassay system (ADVIA Centaur XP, Siemens).

Randomisation and blinding

Computer-generated randomisation sequence with a block size of four (in a ratio of 1:1) was generated by a person who was not involved in the conduct of the study. Patients were randomised to receive either the intervention drug or the placebo according to the sequence. The sequence was kept securely and was planned to be decoded only in case of any serious adverse reactions.

Both the investigators and the patients were blinded to the study intervention. Allocation of patients was done by an investigator using opaque sealed envelope containing either the intervention drug or the placebo.

Endpoints

The primary endpoint was the EMR rate (defined as *BCR-ABL1* transcript level ≤10%, IS) at 3 months of imatinib therapy with and without vitamin D_3 supplementation.

The secondary endpoints were the effect of vitamin D_3 supplementation on CHR, the safety of vitamin D_3 supplementation in patients with newly diagnosed CML-CP on imatinib therapy, and the correlation of the baseline vitamin D_3 levels in patients with CML-CP with CML prognostic scores and treatment response.

Sample size

According to a study done by Jabbour *et al*,[9] EMR in patients receiving imatinib was 64% (at the end of 3

months of therapy). Considering an α of 0.05, desired level of statistical significance (Z 1-α/2) of 1.96, power (β) of 80% (0.8), effect size of 30%, P1 of 94% (intervention group) and P2 of 64% (control group) in the formula, $n=[P1(100–P1)+P2(100–P2)\times z\{(1-\alpha/2)+\beta\}]/(P1–P2)^2$, the sample size in each group was approximated to 25. Accounting for a 10% dropout rate, 31 patients were finally recruited in each treatment group.

Withdrawal criteria

Patients developing hypersensitivity reaction following vitamin D_3 use, hypercalcaemia (total serum calcium >10.5 mg/dL), any new critical illness or any serious adverse events which may affect the outcome of the study were planned to be withdrawn from the study.

Impact of COVID-19 on the study

Telephone communication was done with the patients during the lockdown period. Patients were advised to get the scheduled investigations done at the nearby government hospital or National Accreditation Board for Hospitals & Healthcare Providers (NABH)-accredited laboratories in case of difficulty to travel during the lockdown period. Patients were called up routinely to monitor the occurrence of adverse events, if any.

Statistical analysis

Data were entered in Microsoft Excel V.2013. All statistical analyses were done using STATA V.17. The primary analysis included all randomised patients (ie, intention to treat). All analyses used two-sided tests of statistical significance. Normality assessment was done using Shapiro-Wilk test. Median (IQR) was used to describe non-normally distributed parameters. Comparison of the descriptive variables among the study groups was performed using the two-sample Wilcoxon rank-sum test (Mann-Whitney U test) for continuous variables and χ^2 or Fisher's exact test for categorical variables. Kaplan-Meier curve was used to depict the time taken to achieve CHR in both groups, and the difference among them was analysed with log-rank test.

Trial registration

The trial was registered at Clinical Trial Registry India (CTRI/2019/09/021164).

Patient and public involvement

Before starting the study, intervention procedures, patient information sheet and outcome measures were discussed with a panel of patients with CML to test feasibility, comprehensibility, completeness, and relevance, respectively. Study results were presented to and discussed with the patients with CML to enhance implementation of the results.

RESULTS

Seventy-five patients attending the haemato-oncology outpatient department were screened for eligibility. Among them, 13 did not meet the inclusion criteria. Hence, 62 patients were included in the study (31 patients each in the intervention group and the placebo group) (figure 1).

The median age of the patients was 35 (IQR: 28–45) years, ranging from 16 to 75 years. Among them, 58.1% were male. Splenomegaly was present in 58 (93.5%) patients, where spleen size ranged between 2 cm and 24 cm below the costal margin. The median spleen size was 11.5 cm. Hepatomegaly was present in eight (13%) patients, where liver size ranged between 2 cm and 8 cm below the costal margin. Baseline haematological parameters are summarised in table 1.

Among the study patients, six refused bone marrow aspiration, whereas five had dry tap. In the remaining 51 patients, the classic Philadelphia chromosome, t(9,22) (q34:q11.2), was observed in 46 patients; additional cytogenetic abnormalities were seen in 5 patients [2 in the Imatinib+Vitamin D3 (IMVD) group and 3 in the Imatinib+Placebo (IMP) group]. There was no statistically significant difference between the two groups (p=0.54).

Prognostic risk scoring was done at baseline for all the patients. According to Sokal score, 46.8% had intermediate risk and 45.2% had low risk. According to Hasford score, majority (79.1%) were categorised into low risk. Similarly, European Treatment and Outcome Study (EUTOS) score showed that 54.8% had low risk. The baseline risk difference was not statistically significant between the two groups.

Quantitative PCR for *BCR-ABL1* assessment was done from peripheral blood as per international scale (IS) at the time of enrolment and at the end of 3 months. The median value at baseline was 42.4% (IQR: 31.5–56.3) and at the end of 3 months was 5.76% (IQR: 1.7–9.2) (IS). There was no statistically significant difference between the study groups (p=0.46). At the end of 3 months, 85.5% of the patients were found to achieve CHR. However, there was no significant difference between the two groups (OR 1.3, 95% CI 0.25 to 7.23, p=1.0) (table 2).

Time taken to achieve CHR was assessed in both groups with serial CBC tests and was depicted using Kaplan-Meier curves. A median time of 38.5 (IQR: 32–43) days was taken to achieve CHR. Patients of the IMVD group had taken 38 (IQR: 30–43) days to achieve CHR, whereas patients of the IMP group had taken 40 (IQR: 33–42) days. However, there was no statistically significant difference between the groups (p=0.83) (online supplemental figure 1).

At baseline, overall vitamin D_3 deficiency (levels <20 ng/mL) was seen in 64.5% (61.3% in the IMVD group and 67.8% in the IMP group), among which severe deficiency (<10 ng/mL) was seen in 29% (25.8% in the IMVD group and 32.3% in the IMP group) and vitamin D_3 insufficiency (levels 20–<30 ng/mL) was seen in 35.5% (16.1% in the IMVD group and 25.8% in the IMP group). Normal vitamin D_3 level was seen in only 14.5% of the patients (22.5% in the IMVD group and 6.45% in the IMP group). There was no statistically significant difference among the study groups (p=0.31). At the end of 3 months, overall

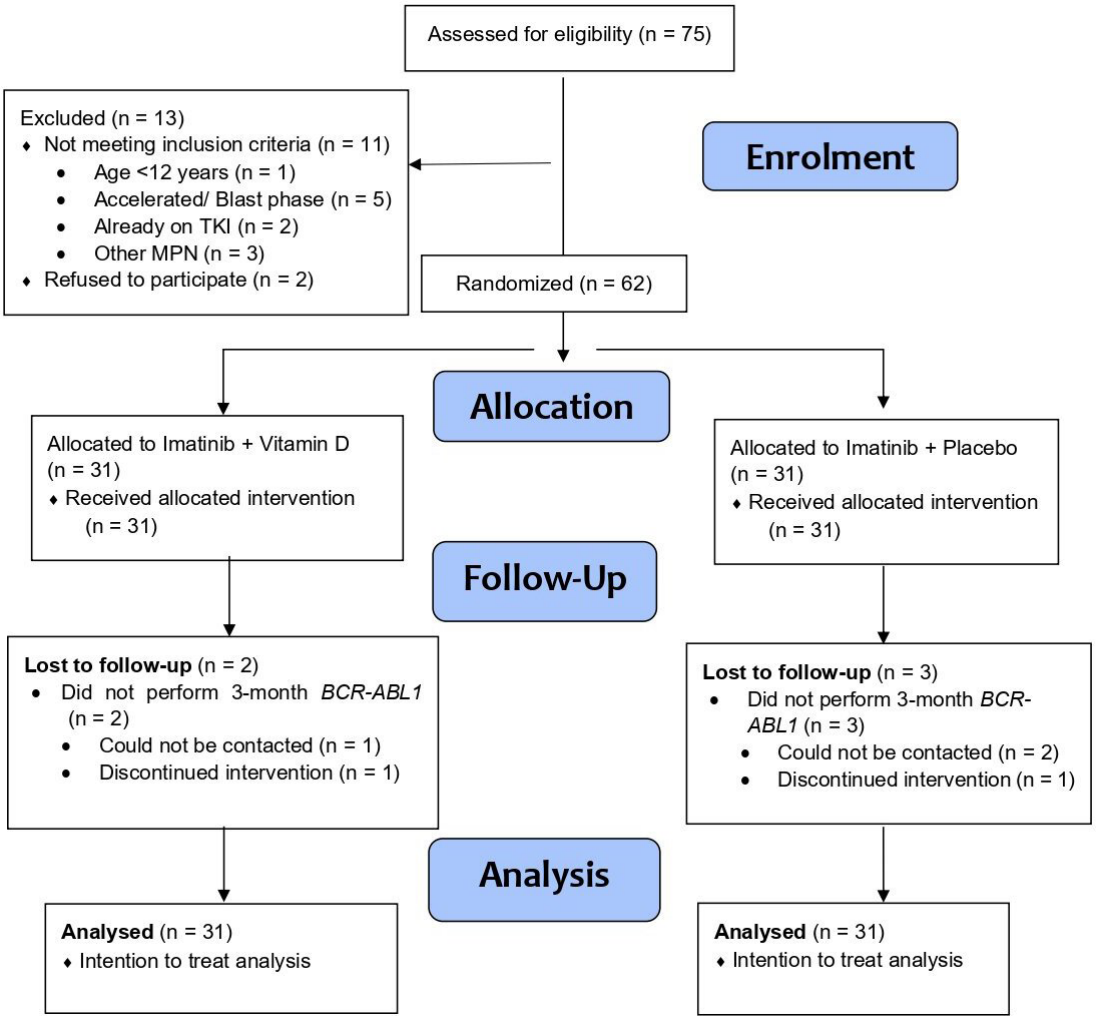

Figure 1 CONSORT flow diagram. CONSORT, Consolidated Standards of Reporting Trials; TKI, tyrosine kinase inhibitor.

vitamin D_3 deficiency was seen in 37.1% (29% in the IMVD group and 45.2% in the IMP group), among whom severe deficiency was seen in 8.1% (3.2% in the IMVD group and 12.9% in the IMP group) and insufficiency was seen in 33.9% (38.7% in the IMVD group and 29% in the IMP group). Patients having normal levels of vitamin D_3 increased from a baseline of 14.5% to 29% (32.3% in the IMVD group and 25.8% in the IMP group) at the end of the study. However, there was no statistically significant difference between the two groups (p=0.4) (table 3).

During the course of the study, 119 adverse drug reactions (ADRs) were reported in 51 study patients. A total of 59 ADRs were noted in 26 patients of the IMVD group, of which 6 were grade ≥3. A total of 60 ADRs were reported in 25 patients of the IMP group, of which 8 were grade ≥3. There was no statistically significant difference between the two study groups (p=0.6). None of the patients was withdrawn from the trial due to ADR (table 4).

Correlation of risk scores with baseline vitamin D_3 levels was done using Spearman correlation coefficient (r_s). The correlation was weakly positive with Sokal score (r_s=0.171, p = 0.18), Hasford score (r_s=0.329, p = 0.08) and EUTOS score (r_s=0.235, p = 0.06). None of the risk scores exhibited statistically significant correlation with baseline vitamin D_3 levels. There was a weak negative correlation between *BCR-ABL1* levels at 3 months and difference in vitamin D_3 levels at 3 months from baseline (r_s=−0.211); however, the correlation was not statistically significant (p=0.10).

DISCUSSION

The present randomised controlled trial was envisioned to explore the role of vitamin D_3 supplementation with the classic imatinib therapy in patients with newly diagnosed CML-CP attending a tertiary care hospital in northern India. This study focused on short-term supplementation of vitamin D_3 to ensure adherence, minimise loss to follow-up and observe the role of vitamin D_3 in achieving EMR.

The median age at presentation was 35 years, ranging from 16 to 75 years. Our study findings were similar to the study by Mishra *et al*[10] (38 years), Kumar *et al*[11] (38 years) and Phukan *et al*[12] (36 years). In the present study, majority of the patients were male (58%), similar to the study done by Mendizabal *et al*[13] (57.1%) and Kumar *et*

Table 1 Summary of baseline characteristics of study patients

Baseline parameters		Total (n=62)	Imatinib+vitamin D_3 group (n=31)	Imatinib+placebo group (n=31)	P value
Age (years)		35 (28–45)	34 (28–40)	38 (29–48)	0.23
Sex, n (%)	Male	36 (58.1)	19 (61.3)	17 (54.8)	0.61
	Female	26 (41.9)	12 (38.7)	14 (45.2)	
Duration of symptoms (months)		1.5 (1-2)	1.5 (1–2)	2 (1–2.5)	0.29
Spleen size (cm below the costal margin)		11.5 (9–15)	12 (10–15)	11 (8–15)	0.63
Liver size (cm below the costal margin)		3.5 (2–6.3)	5 (2–8)	3.5 (2.5–4.3)	0.76
Baseline haematological parameters					
Haemoglobin (g/dL)		10.4 (9–11.8)	10.5 (9–11.8)	10.2 (8.9–12)	0.84
Total leucocyte count ($\times 10^9$/L)		153.5 (105–226.2)	132 (91.5–242)	178.8 (109.2–226.2)	0.54
Platelet count ($\times 10^9$/L)		330.5 (202–458)	349 (185–458)	328 (202–495)	0.72
Peripheral blood blast (%)		3 (2–4)	3.5 (2–5)	2.5 (2–4)	0.37
Neutrophil (%)		45 (39–58)	47.5 (37–55)	44 (39–60)	0.81
Lymphocyte (%)		3 (2–6)	3 (2–6)	3 (2–6)	0.61
Monocyte (%)		2 (1–2)	2 (1–3)	2 (1–2)	0.59
Eosinophil (%)		3 (2–5)	3 (2–4)	4 (2–5)	0.41
Basophil (%)		5 (4–7)	5 (4–8)	5 (4–7)	0.93
Promyelocyte (%) (n=44)		3 (1–4.5)	2.5 (1–5)	3 (2–4)	0.67
Myelocyte (%) (n=60)		23 (16–28)	23 (17–27)	23 (15–30)	0.77
Metamyelocyte (%) (n=56)		10 (7–15)	10 (7–15)	10.5 (7–15)	0.82

All parameters are expressed as median (IQR), except gender which is expressed in n (%).

al[11] (57.2%). The most common symptom among the study patients was abdominal pain, followed by abdominal heaviness and fatigue, similar to the study done by Kumar *et al*[11] and Mishra *et al*.[10]

BCR-ABL1 levels remain the cornerstone of monitoring patients with CML-CP during treatment. After 3 months of treatment, the median *BCR-ABL1* transcript ratio in our study patients was 5.6% IS, with no difference between the groups. A study by Hanfstein *et al*[14] stated the ratio of *BCR-ABL1* as 1.4% at 3 months. The number of *BCR-ABL1* transcripts at 3 months is defined by the level at diagnosis and its change over time after the onset of treatment. The prognostic impact of response at 3 months might be derived either from the steepness of response or from the initial tumour burden.[15]

In our study, EMR (*BCR-ABL1* levels ≤10%) was observed in 78.9% of the patients. In a study by Kim *et al*,[16] 57.5% of the patients had EMR. Our study had patients of younger age as compared with Kim *et al*,[16] which might have contributed to the disparity. In a study

Table 2 Summary of peripheral blood quantitative *BCR-ABL1* and complete haematological response

Variable		Total	Imatinib+vitamin D_3 group	Imatinib+placebo group	P value
BCR-ABL1 (IS) at baseline, median (IQR)		42.4 (31.5–56.3)	46.2 (30.65–56.7)	40.9 (31.5–56.1)	0.76
BCR-ABL1 (IS) at 3 months, median (IQR)		5.76 (1.79–9.2)	5.1 (1.32–8.3)	6.57 (3.2–9.9)	0.46
BCR-ABL1 (IS) at 3 months, n (%)	≤10%	45 (78.9)	24 (82.7)	21 (75)	OR: 1.6, 95% CI 0.37 to 7.37, p=0.4
	>10%	12 (21.1)	5 (17.2)	7 (25)	
CHR at 3 months, n (%)	Yes	53 (85.5)	27 (87.1)	26 (83.9)	OR: 1.3, 95% CI 0.25 to 7.23, p=1.0
	No	9 (14.5)	4 (12.9)	5 (16.1)	

CHR, complete haematological response; IS, international scale.

Table 3 Summary of vitamin D_3 levels in the study groups at baseline and at 3 months

Vitamin D_3 levels (ng/mL) at timepoints	Total Median (IQR)	Imatinib+vitamin D_3 group Median (IQR)	Imatinib+placebo group Median (IQR)	P value
Baseline	13.8 (9.5–24)	13.5 (9.5–27.5)	15.2 (9.5–23.1)	0.77
3 months	23.62 (15.8–33.9)	24.63 (16.2–39.3)	21.7 (11.6–33.3)	0.07
Difference in vitamin D_3 at 3 months from baseline	4 (0.3–14.3)	7.05 (3.2–15.02)	1 (2.4–14.3)	0.01

Table 4 Distribution of adverse drug reactions in the study groups

Adverse drug reactions	Imatinib+vitamin D_3 group n (%)	Grade ≥3 n (%)	Imatinib+placebo group n (%)	Grade ≥3 n (%)	P value
Haematological					
Anaemia	7 (22.6)	1 (3.2)	8 (25.8)	2 (6.5)	0.86
Leucopenia	4 (12.9)	–	3 (9.7)	–	
Thrombocytopaenia	2 (6.5)	–	4 (12.9)	–	
Febrile neutropaenia	1 (3.2)	1 (3.2)	1 (3.3)	1 (3.3)	
Non-haematological					
Nausea/vomiting	10 (32.3)	1 (3.2)	9 (29.0)	2 (6.5)	0.93
Muscle cramps	8 (25.8)	2 (6.5)	8 (25.8)	1 (3.2)	
Fluid retention	8 (25.8)	–	6 (19.4)	–	
Anxiety	7 (22.6)	–	5 (16.1)	1 (3.2)	
Stomatitis/mouth ulcer	4 (12.9)	1 (3.2)	7 (22.6)	–	
Diarrhoea	5 (16.1)	–	4 (12.9)	1 (3.2)	
Headache	2 (6.5)	–	4 (12.9)	–	
Hyperpigmentation	1 (3.2)	–	1 (3.2)	–	

Percentages in parentheses are calculated column-wise in each group (n=31).

by Jabbour *et al*,[9] EMR was attained in 64% of patients on imatinib.

In the present study, vitamin D_3 supplementation was not shown to have any significant effect on achieving EMR at 3 months. About 82.75% of the patients in the IMVD group and 75% of the patients in the IMP group had achieved EMR but the association was not statistically significant. A study by Campiotti *et al*[17] stated that patients with lower levels of vitamin D_3 (<15 ng/mL) had significantly lower major molecular response. Thomas *et al*[18] stated that patients with Philadelphia-positive leukaemia had significant correlation between molecular response and levels of 25(OH)D. A recent cross-domain text mining by Mehra *et al*[19] also reported the possibility of vitamin D_3 deficiency as a tier 3 grade adverse event associated with long-term treatment with imatinib in patients with CML.

Our research showed that 37.1% of patients were vitamin D_3 deficient at the end of the study period (29% in the IMVD group and 45.2% in the IMP group). The non-significant effect of vitamin D_3 supplementation on EMR and CHR could be because of the fact that normalisation of vitamin D_3 levels was attained in only one-third of patients in the intervention group.

The study entails a novel therapeutic approach in the treatment of CML-CP owing to the high rate of vitamin D_3 deficiency among the patients. Loss to follow-up was minimal (8%). No serious ADRs leading to discontinuation of the intervention were found in the present study. However, all the scheduled follow-up visits could not be done owing to the COVID-19 pandemic. Hence, compliance to the intervention was remotely monitored in a few patients during lockdown. Long-term follow-up of the patients could not be done due to the limited study duration of 3 months.

CONCLUSION

In the present clinical trial, vitamin D_3 levels were low among the recruited patients with CML-CP. However, supplementation of vitamin D_3 with imatinib therapy did not have significant effect on EMR or CHR. As existing literature suggests that lower vitamin D_3 levels lead to delayed EMR, further clinical trials could be undertaken to assess the effective dosage and duration of vitamin D_3 supplementation in these patients.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Obtained.

Ethics approval All patients were informed about the purpose of the trial; informed consent was taken and trial was conducted in accordance with the Declaration of Helsinki. The authors confirm that necessary IRB and/or ethics committee approvals have been obtained. The study was approved by the Institutional Ethics Committee (AIIMS/IEC/19/898).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. We have included all the data produced in the present work in the manuscript. Note that raw data are available with the principal investigator. We are unable to attach all the raw data for each participant in this paper due to ethical restrictions.

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