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Optimized Vitamin D Repletion in Refractory Patients Undergoing Stem Cell Transplant with Oral Thin Film Cholecalciferol

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Abstract:
Vitamin D deficiency is common in childhood, pervasive before and after bone marrow transplant, and associated with increased incidence of graft-versus-host disease (GVHD) and decreased survival in patients undergoing hematopoietic stem cell transplantation (HSCT). Numerous barriers impede replacement, including malabsorption secondary to gut GVHD, mucositis, inability to take capsules, kidney disease, liver disease, and infection; many patients remain refractory despite vitamin D therapy. We hypothesized that a different formulation of cholecalciferol, administered on the tongue as a readily dissolving oral thin film (OTF), would ease administration and facilitate therapeutic vitamin D levels (>35 ng/mL) in refractory patients. In this prospective pilot study, we evaluated 20 patients post-HSCT (range: day +21 - day +428 at enrollment) with serum vitamin D levels </=35 ng/mL. Cholecalciferol OTF strips (CURE Pharmaceutical) were administered for twelve weeks. Dosing was based on patient size and titrated according to individual pharmacokinetics. Wilcoxon matched-pairs signed rank test demonstrated marked improvement in all 20 formerly refractory patients, increasing from a median baseline vitamin D of 29.2 ng/mL to 58 ng/mL at end of study ($p<0.0001$). All patients demonstrated improvement in serum vitamin D level by week 4 on study, some of whom had been refractory for years prior. Median dose was 1 OTF strip (40,000 IU) per week. No toxicity was observed. This formulation proved to be safe, effective, efficient, and well-received. We are eager to explore other patient populations which might benefit from this promising development, and other therapeutics which might be optimized by this mode of delivery.

Conflict of interest: No COI declared

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Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: For original data, please contact allison.bartlett@cchmc.org.

Clinical trial registration information (if any): This study was registered on clinicaltrials.gov under the title "Vitamin D Replacement Using Oral Thin Film (OTF) Cholecalciferol in Patients Undergoing Hematopoietic Stem Cell Transplantation," identifier: NCT04818957.

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Title: Optimized Vitamin D Repletion in Refractory Patients Undergoing Stem Cell Transplant with Oral Thin Film Cholecalciferol

Short Title: Dissolvable Cholecalciferol Repletes Vit D in HSCT

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Data Sharing Statement

Study data will be shared in the form of scientific publication as part of our continued, systematic research on Vitamin D in HSCT recipients, with the goal to improve clinical management. Published material will have deidentified data on HSCT recipient demographics, disease features, vitamin D levels, supplementation mode and intervention outcomes. This publication will be immediately available to the research community. For original data, please contact allison.bartlett@cchmc.org.

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Key Points:

- Vitamin D deficiency is pervasive and problematic in hematopoietic stem cell transplant; repletion is poorly tolerated and rapidly catabolized
- We show marked, rapid, sustained improvement in vitamin D levels for 20 patients with novel, oral thin film cholecalciferol formulation

Abstract

Vitamin D deficiency is common in childhood, pervasive before and after bone marrow transplant, and associated with increased incidence of graft-versus-host disease (GVHD) and decreased survival in patients undergoing hematopoietic stem cell transplantation (HSCT). Numerous barriers impede replacement, including malabsorption secondary to gut GVHD, mucositis, inability to take capsules, kidney disease, liver disease, and infection; many patients remain refractory despite vitamin D therapy. We hypothesized that a different formulation of cholecalciferol, administered on the tongue as a readily dissolving oral thin film (OTF), would ease administration and facilitate therapeutic vitamin D levels (>35 ng/mL) in refractory patients. In this prospective pilot study (NCT04818957), we evaluated 20 patients post-HSCT (range: day +21 – day +428 at enrollment) with serum vitamin D levels ≤35 ng/mL. Cholecalciferol OTF strips (CURE Pharmaceutical) were administered for twelve weeks. Dosing was based on patient size and titrated according to individual pharmacokinetics. Wilcoxon matched-pairs signed rank test demonstrated marked improvement in all 20 formerly refractory patients, increasing from a median baseline vitamin D of 29.2 ng/mL to 58 ng/mL at end of study ($p<0.0001$). All patients demonstrated improvement in

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serum vitamin D level by week 4 on study, some of whom had been refractory for years prior. Median dose was 1 OTF strip (40,000 IU) per week. No toxicity was observed. This formulation proved to be safe, effective, efficient, and well-received. We are eager to explore other patient populations which might benefit from this promising development, and other therapeutics which might be optimized by this mode of delivery.

Introduction

The role of vitamin D in bone health and skeletal maturation has long been established, as it facilitates the absorption of calcium and enables normal growth and bone remodeling. However, in more recent medical literature, it has come to light that vitamin D has a widespread and diverse set of biological actions, with receptors scattered throughout the body,[1,2] playing a significant role in many pathophysiological processes. Similarly, vitamin D deficiency has been implicated in an extensive list of severe diseases, and inferior outcomes are often associated with deficiency.[3-6]

Specifically, in our population of patients undergoing hematopoietic stem cell transplant (HSCT), our group has shown that vitamin D deficiency is exceedingly common before, during, and after transplant.[7] Perhaps even more worrisome, the vitamin D deficiency uncovered in this vulnerable population is persistent and associated with decreased overall survival.[7-11] Normal vitamin D levels prior to transplant and in the early post-transplant period have been associated with a lower incidence of graft-versus-host disease (GVHD), lower levels of proinflammatory cytokines and improved immune

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reconstitution.[11-13] With aggressive enteral supplementation, we have been able to significantly improve outcomes and quality of life for many of these children.[7,9,10]

However, the sustainability of improved serum vitamin D levels presents another challenge. The morbidity associated with a hematopoietic stem cell transplant is significant, and often severely impacts the health and function of the gut. Enteral vitamin D supplementation is dependent on passive diffusion of the fat-soluble vitamin across the intestine.[14,15] We previously demonstrated that it is very challenging to achieve and sustain therapeutic vitamin D levels in pediatric HSCT recipients using currently available vitamin D formulations (capsules and liquid), even after assuring patient compliance.[9] Many patients suffering with severe malnutrition, diarrhea and/or gastrointestinal graft-versus-host disease following hematopoietic stem cell transplant are unable to absorb enterally administered vitamin D and are refractory to supplementation, with serum vitamin D levels poorly responsive to ongoing supplementation even after assuring compliance with prescribed therapy. Additionally, with a high incidence of mucositis and severe nausea/vomiting, and many young patients in our population, taking medication capsules is a painful struggle, and often not possible.

We report significant improvement in vitamin D levels in previously refractory patients by using oral thin film (OTF) cholecalciferol, a novel, berry-flavored formulation of vitamin D which dissolves readily when placed on the tongue and has ability to bypass, at least in part, the need for absorption in the gut that allowed our study subjects to achieve and

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sustain normal 25-hydroxy vitamin D (25(OH)D) levels of ≥35ng/mL. OTF formulation also significantly improves the ease of administration, making them well-received by patients and facilitating sustainable therapeutic vitamin D levels.

Methods

Study Design

Our single-site, prospective, pilot study to evaluate the safety, efficacy, and tolerance of oral thin film cholecalciferol in repleting serum vitamin D levels in bone marrow transplant patients was approved by the Institutional Review Board (IRB) at Cincinnati Children's Hospital Medical Center. This study was registered on clinicaltrials.gov under the title "Vitamin D Replacement Using Oral Thin Film (OTF) Cholecalciferol in Patients Undergoing Hematopoietic Stem Cell Transplantation," identifier: NCT04818957. Our primary aim was to achieve and sustain serum 25-OH vitamin D levels >35 ng/mL during a 12-week study period of vitamin D supplementation. This level was based on the Endocrine Society guidelines for bone metabolism defining 25-OH vitamin D level <30 ng/mL as insufficient, where 25-OH vitamin D levels of 30-40 ng/mL are required for physiologic affect via parathyroid hormone.[16]

Patient Selection

We aimed to evaluate 20 patients who had undergone or were undergoing HSCT with 25(OH)D levels ≤35 ng/mL, or who had been unable to tolerate/refractory to standard enteral supplementation. Inclusion criteria were HSCT recipients of any age with vitamin D levels ≤35 ng/mL, or unable to tolerate, or refractory to enteral supplementation

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formulations of Vitamin D. Inability to take prescribed vitamin D formulation or non-compliance was confirmed by reviewing nursing documentation in medical records. Patients could be undergoing HSCT or have completed HSCT at any time in the past, both inpatients and outpatients were eligible to enroll. Exclusion criteria were any subjects with vitamin D level ≥100 ng/mL, and any patients with clinically significant and uncontrolled hypercalcemia. Written, informed consent to participate was obtained from each enrolled subject and/or legal guardian. It is important to note that patients enrolled onto this study had been on enteral supplementation and had remained vitamin D deficient despite using other vitamin D formulations in escalating doses for 3-23 months prior to this study. In addition, all study subjects had received single ultra-high dose vitamin D (Stoss therapy) at the start of HSCT without adequate or sustained response.[10] Stoss therapy, from the German “to push,” is a single mega-dose of vitamin D which has been proven to be effective in repleting vitamin D levels in many chronic diseases. Stoss dose in our HSCT recipients had been administered as a single dose based on patient weight and serum vitamin D level, with maximum dose limit of 600,000 IU, as previously published.[10]

Vitamin D OTF Supplementation and Outcome Measurement

Baseline serum vitamin D (25-OH vitamin D), calcium and phosphorus were obtained on all patients. These levels were monitored throughout enrollment, weekly for the first four weeks, and at least monthly thereafter, with more frequent evaluations performed as clinically indicated. End of study serum vitamin D levels were obtained within 2 weeks after final OTF administration. Serum vitamin D levels were measured by

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chemiluminescent immunoassay (CLIA) and all other blood tests were performed utilizing biochromatic endpoint technique.

All subjects stopped other forms of vitamin D supplementation at study entry when starting on vitamin D OTF. Supplementation with cholecalciferol OTF strips (CURE Pharmaceutical, Oxnard, CA) was initiated based on patient weight, in accordance with institutional standard of care. Each OTF strip contains 40,000 IU Vitamin D3 (1000 mcg cholecalciferol). Patients weighing <40kg at the time of enrollment received 1 strip for their initial dose, patients weighing ≥40kg at the time of enrollment were started on 2 strips. Dosing was titrated based on response and pharmacokinetics of the individual, in accordance with our dosing schema shown in **Figure 1**, based on prior institutional experience.

Patients on the inpatient ward or receiving their dose in outpatient clinic were observed by medical staff to verify ingestion. Vitamin D OTF strips were berry-flavored and dissolved readily when placed on the tongue; patients were permitted to take a small sip of water immediately before or after strip dissolved as desired. Outpatients taking OTF strips at home maintained a study diary to document dosing. Patients were required to complete at least 6 weeks of the 12-week study to be considered evaluable. Patients with clinically significant and/or uncontrolled hypercalcemia were excluded from the study.

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Each subject received OTF strips for a maximum of 12 weeks, with the ability to stop supplementation at the discretion of the physician if vitamin D level was adequate and additional supplementation was not needed. Any patients with difficulty tolerating the OTF could have their dose adjusted or discontinued at the discretion of the physician.

Clinical Care

Routine clinical care for patients during and after HSCT was continued for all subjects, in accordance with institutional standards of care. All patients on study were concurrently managed by a registered dietitian.

Statistical Analysis

Continuous data were summarized according to their median values. Differences in outcomes were compared by using a Wilcoxon matched-pairs signed rank test. Statistical evaluation was performed using GraphPad Prism (Version 9.2.0). $P < 0.5$ was considered statistically significant.

Data Sharing Statement

Study data will be shared in the form of scientific publication as part of our continued, systematic research on Vitamin D in HSCT recipients, with the goal to improve clinical management. Published material will have deidentified data on HSCT recipient demographics, disease features, vitamin D levels, supplementation mode and intervention outcomes. This publication will be immediately available to the research community. For original data, please contact allison.bartlett@cchmc.org.

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Results:

Study population

A total of 24 patients were enrolled on the study, with a goal of 20 evaluable patients. Four patients were not evaluable: two patients had to take multiple OTFs for each dose and disliked the texture with repeated administration, one disliking the taste and one due to parental non-compliance.

Evaluable patient demographics and disease characteristics are summarized in Table 1. Among our patient population, some patients were refractory to Stoss therapy (n=6), some were refractory to Stoss therapy and enteral supplementation (n=10), while others were unable to tolerate enteral supplementation formulations (n=4). Fourteen patients had underlying clinical conditions or transplant complications predisposing to impaired intestinal absorption: thrombotic microangiopathy (n=6), inflammatory bowel disease (n=3), pancreatic insufficiency (n=2), malacoplakia (n=1), stage 4 intestinal GVHD (n=1), and history of gastrointestinal vaso-occlusive crisis (n=1).

Efficacy of OTF Cholecalciferol on Serum Vitamin D Levels in HSCT Patients

Twenty patients were evaluable. Median number of weeks on study for these 20 patients was 12 weeks. There were two patients in our cohort who did not complete all 12 weeks; one patient unexpectedly relapsed post-transplant, and family preference was to come off study at that time (8 weeks), and another patient returned to their home institution prior to completion (9 weeks). Serum vitamin D levels of our cohort on study

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are outlined in **Table 1.** The median age of our cohort was 8 years old (range: 1-28 years).

All study subjects achieved the primary study endpoint to reach and to sustain 25-OH vitamin D serum level ≥35ng/mL. Study subjects' serum vitamin D levels improved from a baseline median 29.2 ng/mL (range: 23.9 – 35.8 ng/mL) at enrollment to 58 ng/mL (range: 36.7 – 100.8 ng/mL) ($p<0.0001$) at end of study (**Figure 2**).

Median improvement of vitamin D levels on study was an increase by 29 ng/mL, effectively doubling baseline vitamin D levels at end of study. All twenty patients demonstrated improved vitamin D levels within the first four weeks, with consistent median values on study of 53 ng/mL (range 40.8 – 54.1 ng/mL) (**Figure 3**). Some patients' levels escalated quickly prompting dose reduction to maintain target levels. The dosing schema was updated following enrollment of the first few patients secondary to the rapid absorption observed. Median dose for our cohort was 40,000 IU (1 strip) per week. Doses of vitamin D during the twelve weeks on study ranged from 40,000 IU monthly to 160,000 IU weekly.

Tolerance and Toxicity of OTF Cholecalciferol

Ability to take vitamin D OTF and compliance with prescribed study therapy was documented by nursing staff in medical records or reported to study staff by caregivers for those receiving OTF at home. OTF strips were well-received by patients of all ages, with palatable flavor and rapid dissolution. Subjects who were enrolled onto study due

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to intolerance or non-compliance of other vitamin D formulations were documented to have good compliance with OTF. Eight study subjects (40%) were younger than 5 years of age, with four of them being younger than 2 years of age, and all were able to successfully take the OTF strips, which dissolved within seconds and did not need to be swallowed. Peak median vitamin D levels for the cohort were noted at week five on study, at 64.7 ng/mL, and these results were well sustained over the remaining weeks on study. Maximum serum vitamin D level on study was 118 ng/mL, trending down to 65.3 ng/mL the following week. No toxicity was noted for any of the patients on study, elevations observed >100 ng/mL were noted for one week only. Concurrent monitoring of renal panels, including calcium and phosphorus levels, did not demonstrate any concerning elevations. There were no adverse events attributable to the study drug while taking the vitamin D OTF strips.

Discussion:

This prospective pilot study demonstrates the safety and efficacy of a novel formulation of cholecalciferol, administered as a readily dissolvable oral thin film (OTF), for repletion and maintenance of therapeutic serum vitamin D levels in HSCT patients refractory to other available vitamin D formulations. The vitamin D OTF strips were also very efficient in repleting serum vitamin D levels, with all patients achieving therapeutic vitamin D levels (>35 ng/mL) by week 4. Improved levels were likewise sustained throughout 12 weeks on study, with median serum vitamin D levels on study ranging from 40.8 – 54.1 for all 20 patients. This was especially noteworthy for patients who had been refractory to enteral supplementation using other formulations of vitamin D supplements for

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months to years prior to this study enrollment, yet rapidly achieved therapeutic vitamin D level after switching to comparable dosing with OTF formulation.

In addition to noting marked improvement in serum vitamin D levels for all patients enrolled, OTF administration was easy, readily dissolved without need for swallowing, and was well-received by patients of all ages on study. Patients who reported disliking OTF had to take multiple OTF strips for a single dose. We adjusted our strategy giving one OTF at a time with a short break in between strips and resolved this issue. There were no complaints from patients taking one OTF strip at a time. Numerous patients and families expressed how much they enjoyed the flavor and ease of this formulation. They also expressed a preference for the OTF formulation, and an interest in being able to continue OTFs at the completion of the 12 weeks of study. The wide range of ages enrolled highlights the versatility of this mode of delivery, with our youngest patient tolerating strips at just 13 months of age, and our oldest patient at 28 years of age.

It is well known that bioavailability of vitamin D differs among individuals due to variable absorption or altered metabolism in the body. Oral Vitamin D formulations are influenced by several different factors after ingestion including gastric pH, gastric enzymes including pepsin and trypsin, and duodenal enzymes like proteases, amylase, and lipase. Our patient cohort was enriched with cases prone to prolonged impaired bowel and/or pancreatic function due to their underlying pre-transplant conditions, like Shwachman-Diamond syndrome, immune deficiencies with inflammatory bowel disorder, or transplant complications like intestinal GVHD and intestinal thrombotic

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292 microangiopathy, that rendered these patients vitamin D deficient even later post-
293 transplant.
294
295 This new vitamin D OTF formulation is absorbed, at least in part, through the oral
296 mucosa directly into the blood stream, bypassing the first-pass hepatic metabolism. It
297 also does not cause additional discomfort in patients with mucositis due to fast
298 dissolution and no need to swallow. This is very appealing in a complex patient
299 population like HSCT recipients with altered GI tract function. OTF also lightly adheres
300 to the tongue while being dissolved by saliva, likely contributing to improved mucosal
301 absorption. Administration of OTF is straightforward for caregivers, readily observed,
302 reliably absorbed and well-tolerated. For these reasons, OTF is desirable compared to
303 other liquid formulations, especially for young children.
304
305 As could be expected, pharmacokinetics in our study population were patient
306 dependent, likely multifactorial, with significant variability in dosing required to achieve
307 vitamin D repletion. In our cohort this variability was not strictly related to patient age or
308 weight, but likely related to a patient's clinical condition. We observed ongoing
309 increases in serum vitamin D levels up to 2-4 weeks following administration of a dose.
310 We drew weekly vitamin D levels for the first 4 weeks to learn vitamin D OTF kinetics in
311 our study subjects. The majority of patients achieved and sustained therapeutic vitamin
312 D levels by using 1 OTF strip per week (40,000 IU/week), although we noted a wide
313 range of needs, with patients on study requiring between 1 strip/month (40,000
314 IU/month) up to 4 strips/week (160,000 IU/week). This supports our prior observations

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315 that monthly monitoring of vitamin D kinetics is essential in HSCT recipients, especially
316 early post-transplant.
317
318 In spite of the variability noted in our study in dosing amount and frequency, there were
319 no instances of vitamin D toxicity in our cohort. There is significant variability in the
320 literature concerning levels at which vitamin D toxicity is observed, ranging from 120 –
321 300 ng/mL,[2,17-19] with serum levels demonstrating poor correlation with calcium levels
322 and clinical symptomatic presentation. In general, toxicity is observed in subjects only
323 with sustained, prolonged elevations in their serum vitamin D levels. Common signs and
324 symptoms of vitamin D toxicity include nausea, vomiting, anorexia, diarrhea, bone pain,
325 fatigue, weakness and nephrolithiasis.[2,17,18,20,21] Severe cases involving seizure, coma
326 and even death have been reported.[18] In our cohort, three patients out of twenty were
327 noted to have serum vitamin D levels >100 ng/mL, with a maximum of 118 ng/mL,
328 though none of these levels were sustained longer than 7 days nor were they
329 associated with any clinical symptoms of toxicity. Serum calcium and phosphorus were
330 normal throughout.
331
332 While our prospective pilot study includes only 20 patients, the wide range of ages
333 represented helped to answer essential study questions about efficacy, tolerance, and
334 compliance across different age groups. Based on the promising results of this study,
335 vitamin D OTF has been approved as a formulary option for HSCT recipients at our
336 institution. We are encouraged by the efficacy and ease of administration utilizing an
337 oral thin film formulation for treatment of vitamin D deficiency. This novel mode of

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delivery was especially helpful in this vulnerable population of HSCT patients, who experience many barriers surrounding medication absorption and compliance secondary to complications encountered post-bone marrow transplant. We are eager to explore other important therapeutics for this vulnerable patient population which might be optimized by this mode of delivery. We are additionally working to collaborate with clinicians who care for patient populations with similar challenges and barriers to vitamin D repletion, like patients with short gut, Crohn's disease, celiac disease, and cystic fibrosis to further expand the reach of this novel, exciting and promising therapeutic.

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Author Contributions:

A.B., G.W., K.M. A.T-C., C.T., B.P., R.D., S.D. and S. J. designed the research. A.B., G.Z., G.W., S.M., A.T-C., C.T. and S.J. performed research. B.P. and R.D. supplied drug. A.B. G.Z., G.W., S.M., K.M., A.T-C., C.T., S.D. and S.J. analyzed data. All listed authors contributed to writing the paper.

Conflict of Interest Disclosures:

Study drug was provided by Cure Pharmaceutical at no cost to study subjects.

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SJ holds US patent No: US 10,815,296 B2, lead PI for NIH funded multi-institutional study investigating TA-TMA (R01HD093773) and received travel support and honoraria for lectures from Omeros, Alexion and Sobi (all unrelated to this project).

KM has an investigator initiated clinical trial sponsored by Incyte and serves as the primary investigator of an industry sponsored Elixirgen trial (both unrelated to this project).

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425

426 Figure Legends:

427 **Table 1. Patient demographics and serum vitamin D levels**

Patient	Sex	Age	Weight (kg)	Diagnostic Group	Autologous/Allogeneic Transplant	Vitamin D STOSS dose prior to HSCT?	Additional enteral cholecalciferol supplementation post-STOSS at enrollment?	Enrollment timing post-transplant	Median serum vitamin D (ng/mL) in the year prior to starting strips?	Baseline serum vitamin D (ng/mL)	Median serum vitamin D on study (ng/mL)	End o study serum vitam D (ng/m
1	M	18 yrs	59.6	Malignancy	Allogeneic	Y	Y: 50,000 IU/week	Day +225	26.3	30.1	52.6	69.1
2	F	5 yrs	16.3	Benign Hematology	Allogeneic	Y	Y: 50,000 IU/week	Day +112	27.9	24.6	53.2	77.9
3	F	20 mo	13.0	Malignancy	Autologous	Y	Y: 5,000 IU/week	Day +31	31.7	26.1	53.4	54.4
4	M	4 yrs	19.5	Immune Disorder	Allogeneic	Y	Y: 50,000 IU/week	Day +34	43.0	25.0	53.0	67.0
5	F	9 yrs	20.5	Immune Disorder	Allogeneic	Y	N	Day +26	41.0	34.6	54.1	39.4
6	M	17 yrs	65.1	Malignancy	Allogeneic	Y	Y: 50,000 IU/week	Day +52	29.8	29.7	52.2	82.5
7	M	7 yrs	21.4	Malignancy	Allogeneic	Y	Y: 50,000 IU/week	Day +21	50.5	35.8	52.4	100.
8	M	8 yrs	25.6	Immune Disorder	Allogeneic	Y	Y: 50,000 IU/week	Day +328	33.8	34.6	52.2	41.6

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9	F	28 yrs	47.0	Marrow Failure	Allogeneic	Y	N	Day +64	28.9	29.0	53.0	51.4
10	F	16 mo	11.1	Marrow Failure	Allogeneic	Y	N	Day +156	33.2	30.5	53.0	60.4
11	F	9 yrs	24.7	Malignancy	Allogeneic	Y	Y: 50,000 IU/week	Day +428	31.0	27.9	53.0	42.3
12	M	4 yrs	17.3	Marrow Failure	Allogeneic	Y	N	Day +75	37.5	25.1	52.2	48.5
13	M	19 yrs	88.9	Malignancy	Allogeneic	Y	N	Day +24	20.6	28.0	52.1	36.7
14	M	18 yrs	36.5	Malignancy	Allogeneic	Y	Y: 50,000 IU/week	Day +296	34.5	26.5	53.5	64.0
15	M	9 yrs	22.7	Benign Hematology	Allogeneic	Y	N	Day +75	29.4	29.4	53.4	45.1
16	M	22 yrs	77.9	Immune Disorder	Allogeneic	Y	Y: 50,000 IU/week	Day +19	29.8	23.9	53.7	55.5
17	M	13 mo	8.5	Immune Disorder	Allogeneic	Y	N	Day +50	36.6	33.9	53.5	42.5
18	M	2 yrs	8.7	Marrow Failure	Allogeneic	Y	Y: 50,000 IU/week	Day +71	33.2	33.2	52.2	62.3
19	M	8 yrs	20.5	Benign Hematology	Allogeneic	Y	N	Day +96	35.5	35.0	48.2	70.7
20	M	4 yrs	19.5	Malignancy	Allogeneic	Y	Y: 10,000 IU/week	Day +52	40.5	24.5	40.8	86.4

Figure 1. Vitamin D OTF Dosing Schema

Figure 2. Weekly patient vitamin D levels are shown at baseline through 12 weeks on study. Each blue dot represents one patient. Median values each week shown in red.

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Figure 3. Individual patient serum vitamin D levels are shown at baseline, median while on study and end of study, demonstrating marked improvement. Vitamin D levels doubled across the 12 weeks on study.

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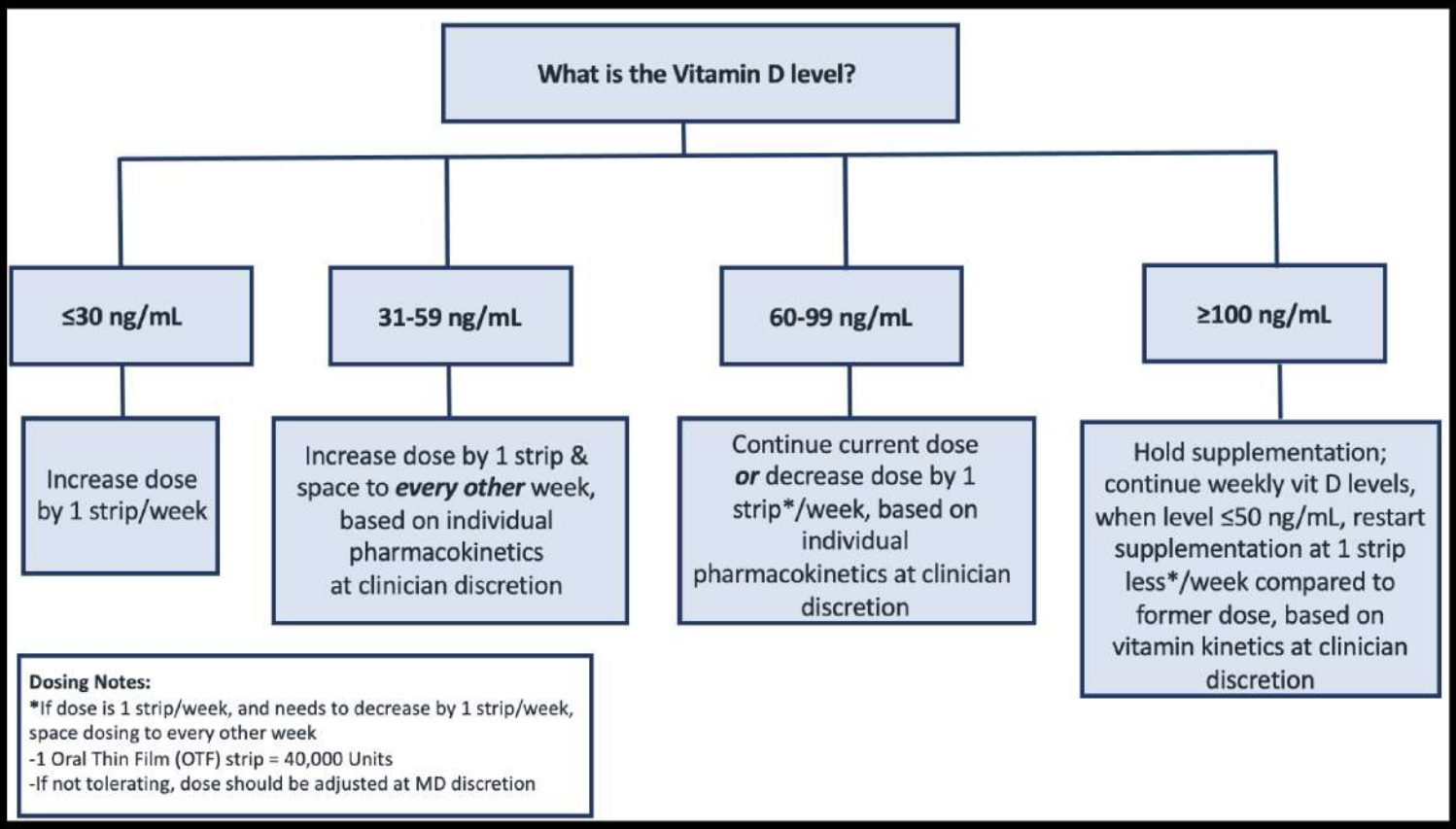
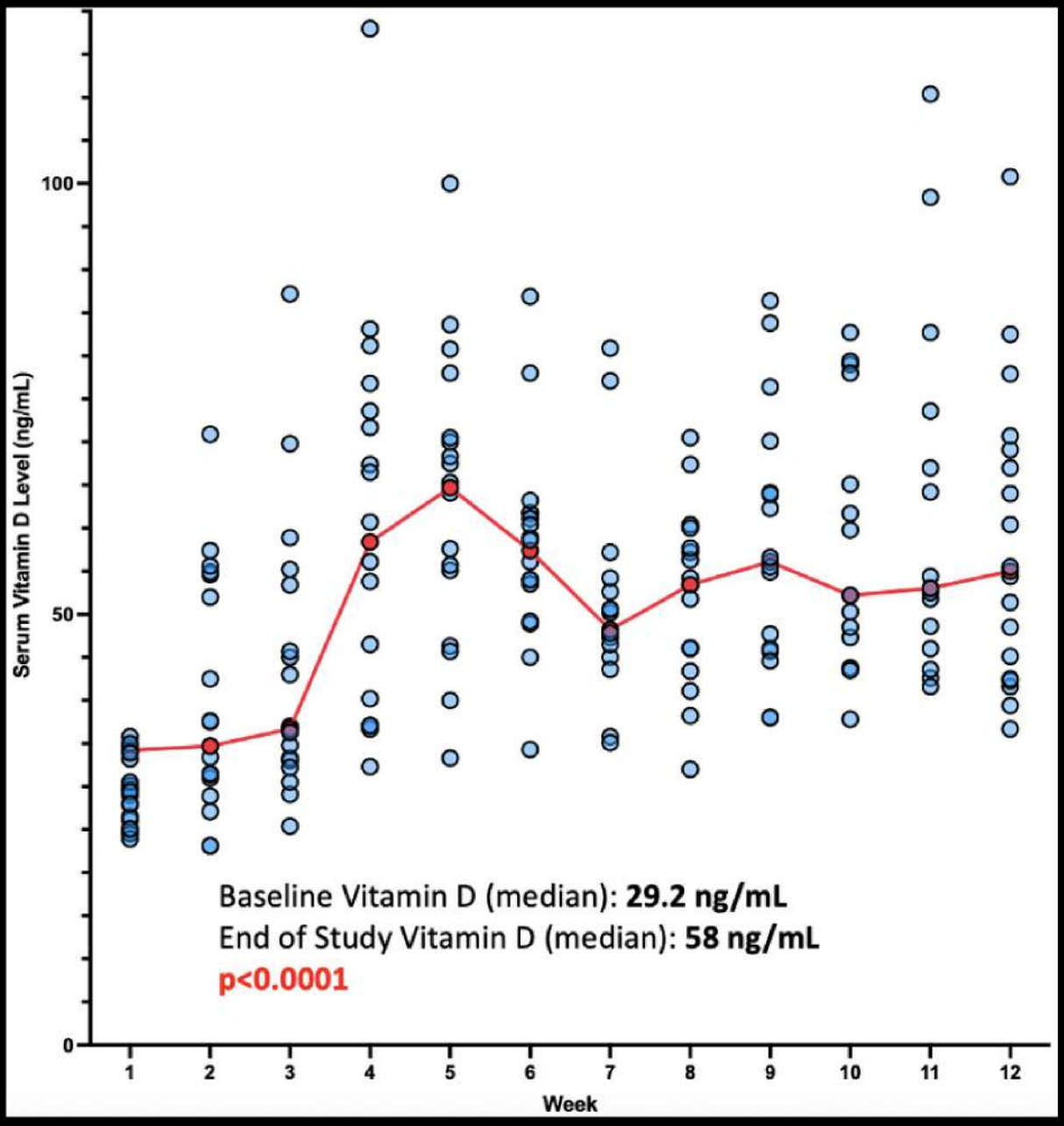
Figure 1.



Vitamin D OTF Dosing Schema

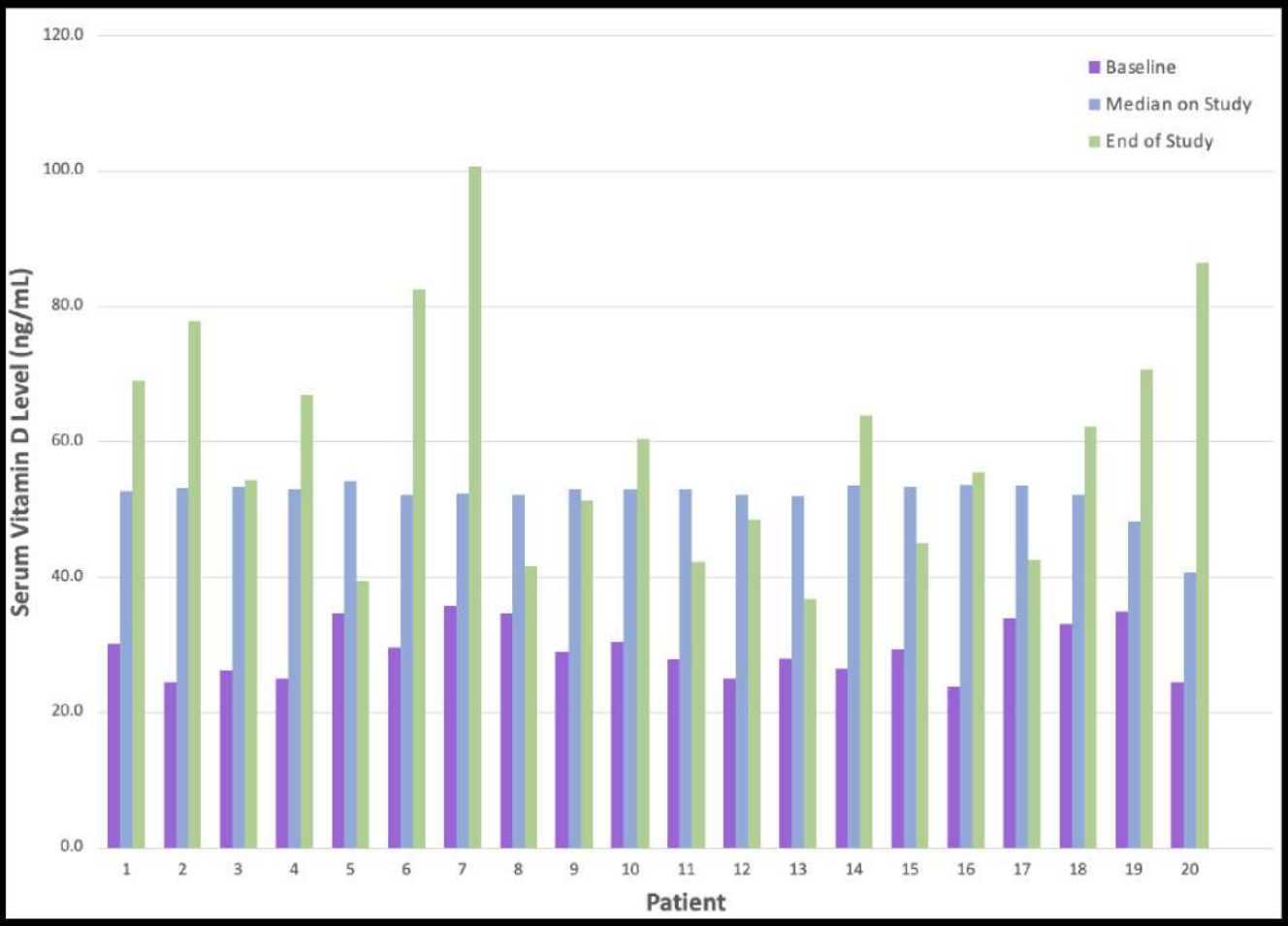
Figure 2.



Weekly patient vitamin D levels are shown at baseline through 12 weeks on study.

Each blue dot represents one patient. Median values each week shown in red.

Figure 3.



Individual patient serum vitamin D levels are shown at baseline, median while on study and end of study, demonstrating marked improvement. Vitamin D levels doubled across the 12 weeks on study.