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Vitamin D Supplementation to Prevent Redevelopment of Basal Cell Carcinoma (BCC): A Phase III Randomized Clinical Trial Protocol

I.Cosgarea[1#*], Y. Chemale[2#*], K. Ahmed[3#*], ME. Gunduz[4], JJ. Rodriguez[5], MJ. Rodriguez[6], L. Leonardo[7], JA. de Oliveira[8], DS. Schwartz[9], A.Tamayo[10], A. Dhawan[11], BM. Mejia[12], L. Schonhaut[13], VO. Olvera[14], TPA. Fernandes[15], FJ. Coimbra[16], VJ. Crestani[17], FA. Machado[18], P.Guimarães[19], G.Constantinescu[20,21]

#These authors have contributed equally to this work.
**Corresponding authors: I. Cosgarea,MD, ioana.cosgarea@newcastle.ac.uk; Y. Chemale,MD, ytchemale@gmail.com; K. Ahmed,MD, drhanfuli@hotmail.com.*

Rest of author's affiliation at the end of the manuscript.

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Abstract:

Introduction: *Basal cell carcinoma (BCC) is the most common non-melanoma skin cancer and a serious disease leading to increased morbidity and high medical costs worldwide. Despite the high recurrence rate of BCCs, the current standard of care consists of regular skin check-ups, with no know therapy to prevent the recurrence. Vitamin D is a safe, affordable, and easily available supplement used for various diseases. There is evidence suggesting its potential use in preventing BCCs, with studies showing that it inhibits the Hedgehog (HH) signaling pathway, an important stimulator of carcinogenesis and the main pathway in BCC development. The objective of this study is to determine the effect of oral vitamin D supplementation on the prevention of BCC redevelopment.*

Methods: *This study is a phase III, multicenter, randomized, placebo-controlled, triple-blinded, superiority trial with two parallel groups on 1:1 allocation of 1746 patients with a previous diagnosis of BCC. The patients will either receive 1000 IU of Vitamin D daily or placebo. During the three-year follow-up period, patients will be undergoing skin check-ups every six months, with annually laboratory tests. The primary endpoint will be the development of further BCC for 3 years after the initiation of vitamin D supplementation. The statistical analysis will be a time-to-event approach, the event being the development of a BCC.*

Discussion: *This is a triple-blinded, randomized, placebo-controlled trial for prevention of a highly prevalent condition. Vitamin D would be a simple solution to prevent the development of further basal cell carcinoma, having a positive effect not only by improving the quality of life of patients, but also by reducing the financial burden on health care systems.*

Keywords*: basal cell carcinoma, vitamin D, phase III randomized trial, trial protocol*

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INTRODUCTION

Basal cell carcinoma (BCC) is the most common non-melanoma skin cancer in the world (Christenson et al., 2005; Karagas, Greenberg, Spencer, Stukel, & Mott, 1999; Lomas, Leonardi-Bee, & Bath-Hextall, 2012) with over 2.8 million new cases diagnosed each year in the United States (Gould & Missailidis, 2011). There is a high incidence of development of secondary BCCs with a 3-year cumulative risk ranging between 33% and 70% (Marcil & Stern, 2000; Telfer, Colver, Morton, & British Association of, 2008), a tenfold increase when compared with the general population. Asides the morbidity involved with BCCs, there is also a great financial burden for health care systems, as it is the fifth most costly cancer to treat in the US (Guy, Machlin, Ekwueme, & Yabroff, 2015; Rogers et al., 2010). Currently, there is no treatment or effective intervention available in preventing BCC redevelopment.

Vitamin D is a hormone involved in a multitude of diseases ranging from infections, diabetes, inflammation, to cancer (Sassi, Tamone, & D'Amelio, 2018). Studies have shown that Vitamin D induces the inhibition of the Hedgehog (HH) signaling, an important stimulator of carcinogenesis and the main pathway in BCC development (Bijlsma et al., 2006; Hahn et al., 1996; Jacob & Lum, 2007; Tang, So, & Epstein, 2007; Tang et al., 2011).

The relationship between vitamin D and cancer development has been debated for a long time. While some observational studies point to a deleterious effect, there is also evidence that suggests that oral vitamin D could decrease the risk of skin cancer (Burns, Elmets, & Yusuf, 2015; Reddy, 2013). The literature is scarce for studies investigating the role of vitamin D for BCC prevention. To our knowledge, there are no large randomized controlled trials that have been conducted to address this medical problem. There is an urgent need to further investigate this knowledge gap to prevent this serious disease.

The primary objective of this trial is to determine the effect of oral vitamin D on the prevention of BCC redevelopment. We will also perform genetic profiling of excised tumors for further mechanistic insights on genes involved with in the carcinogenesis and mutations regarding vitamin D receptor polymorphism. Vitamin D would be a simple solution to prevent the development of further basal cell carcinoma, having tremendous positive effect not only by improving the quality of life of patients, but also by reducing the financial burden on health care systems.

MATERIALS AND METHODS

Trial Design & Study Setting

This study is a phase III, randomized, placebo-controlled, triple-blinded multicenter superiority trial with two parallel groups involving five academic and community hospitals throughout the United States of America (U.S.A). The primary endpoint will be the development of further BCC during 3 years after the initiation of vitamin D supplementation or placebo. The target population will be patients who had a history of BCC.

Randomization

Participants will be randomly assigned to either control or experimental group with a 1:1 allocation as per a central computer-generated randomization schedule using randomly permuted blocks of 4 and 6.

All participants who give consent and fulfill the inclusion criteria will be randomized.

Blinding and Unblinding

The capsules will be produced at a central pharmacy to ensure the similarities in appearance and taste between the placebo and vitamin D. The medication will be given to the patients on the day of the study visit by the research personnel. All trial participants, care providers, investigators, data collectors, and outcome assessors will be masked for the allocation of the patients.

Unblinding will only occur in cases of severe (adverse events AE at least grade 3 according to NCI CTCAE (National Cancer Institute – Common Terminology Criteria for Adverse Events) or life-threatening adverse events. These cases will be discussed with the DMSC (Data Management Safety Committee) and a toll-free line will be available 24 hours for emergency situations. Patients who are unblinded will remain in the study for intention-to-treat analysis.

AE will be assessed at each study visit by the study personnel. Patients will be provided with an emergency contact number which that used in case of suspicion of an AE. AEs will be documented in the electronic case report forms (CRF) and will be used for descriptive statistics.

Participants

Eligible trial participants consist of individuals over 40 years of age, previously diagnosed with a BCC and normal vitamin D levels (between 30ng/mL to 150ng/mL). Exclusion criteria will include the following:

- Excision of the last BCC longer than 3 months from the date of study enrollment
- Vitamin D insufficiency (between 20ng/ml and 30ng/mL) or deficiency (below 20ng/mL) or hypervitaminosis D (greater than 150 ng/mL)
- Any vitamin D usage (one month before randomization)
- Comorbidities with effect on vitamin D metabolism, absorption or excretion: chronic kidney disease, chronic liver disease, hyperparathyroidism, osteoporosis, genetic syndromes
- Patients receiving medications or treatments that affect vitamin D metabolism (immunosuppressives)
- Pregnancy or lactation

Intervention

The intervention is the oral administration of 1000 IU of Vitamin D (group A) or placebo capsules (group B) daily over a period of 3 years.

Study outcomes

The primary outcome will be the development of a new BCC during the intervention. The development of BCC will be assessed every 6 months through skin screenings, in

case of suspicious lesions a skin biopsy will be performed for diagnostic purposes.

As secondary outcomes, the development of further skin cancers such as squamous cell carcinoma, keratoacanthoma, and melanoma will be assessed in the same study period. The development of further skin cancers will be assessed every 6 months through skin screenings, in case of suspicious lesions a skin biopsy will be performed for diagnostic purposes.

Primary and secondary outcome time point being 3 years since study initiation.

Recruitment Strategy

Patients will be recruited in the five centers in the U.S.A. The following recruitment strategies will be used: dissemination of the study information to health professionals via email and official letters, during relevant scientific meetings and through local and national healthcare societies; broad patient information campaign about the trial during social events from skin cancer support groups, and social media advertising (e.g. Facebook, Instagram, Google ads). Additional information about the trial will be given to the pre-screened patients in a scheduled interview.

The recruitment will be carried out until the achievement of the calculated sample size, in a maximum period of 12 months.

Adherence

As a strategy to remind patients to take the medication regularly, a cell phone application and monthly reminding phone calls will be used. Patients will be encouraged to complete a medication diary and bring it to every hospital visit. Calendars and medication bottles will be evaluated, and pills will be counted at each study visit to assess adherence.

Patients will undergo skin screening every 6 months (figure 1). Blood samples will be examined every 12 months and will include vitamin D determination using liquid chromatography/tandem mass spectrometry (LC-MS/MS).

LC-MS/MS is an innovative technique, showing utility in investigating a range of steroidogenesis disorders, offering the advantage of more accurate measurements than immunoassays.

Sample Size

We calculated that 636 events, defined as histological confirmation of BCC redevelopment, would be required in order to detect a development rate reduction of 20% in the exposed group, with power at 80% and alpha at 5%, accounting for a 30% dropout rate. Using the mean 3-year cumulative risk of developing a second BCC of 56% (Marcil & Stern, 2000), the total sample size needed will be 1746 patients, 873 in each group.

Statistical analysis

The statistical analysis will be conducted using STATA 15.1 (Copyright 1985-2017 StataCorp LLC, Statistics/DataAnalysis, StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA). P-values <0.05 will be used for the entire tests carried out for the statistical analysis of this trial.

The primary outcome, redevelopment of BCC, will be analyzed using the Kaplan-Meier curve, time-to-event occurrence and Log-Rank test.

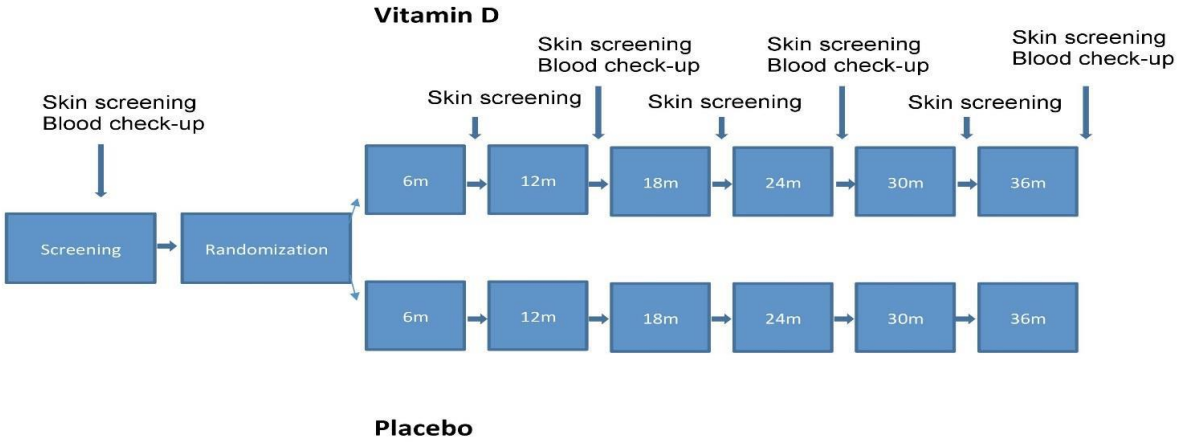

Figure 1. Study Protocol Design. Regular blood check-up will be consisting of vitamin D determination.

The secondary outcome, development of other skin cancer types, will also be assessed using the Kaplan-Meier curve, time-to-event occurrence and Log-Rank test. The Cox Proportional-Hazards Model and Intention-to-Treat (ITT) analysis will be used.

Data Management

The trial will gather all the necessary information from the study participants according to the International Conference of Harmonization standards. All identifiable data will be stored separated from the study data. CRFs will be filled out for every patient by the study personnel. To protect the confidentiality of each subject, numbers assigned to each file will be used for identification of the participants. Files will be maintained in storage for a period of 10 years after completion of the study. It is strictly prohibited to use the data archived for any unauthorized purpose in any other research.

Data monitoring

Periodic inspection for accuracy of the data will be conducted by an independent data safety and monitoring board. This committee will be allowed to make any suggestions for changes or study discontinuation in case of non-adherence to the protocol. The suggestions will be reported and discussed with the principal investigator, the study coordination and the trial sponsor.

IRB Submission

The study protocol will be submitted to local Institutional Review Board (IRB) for approval.

DISCUSSION

Basal cell carcinoma is the most frequent cancer in fair skin individuals (Christenson et al., 2005; Karagas et al., 1999; Lomas et al., 2012) with a high rate of developing further BCCs. So far, the standard of care for patients with previous BCC is just regular skin screenings with no drug or intervention that could prevent the formation of further such tumors. The prevention of this disease represents an unmet challenge that affects not only the health care system, but it also influences the patients' quality of life. Thus, this clinical trial is of paramount importance for identifying a possible drug for secondary prevention of BCC that could impact the clinical practice.

Up to date there are several studies in animal models that offer supporting data that vitamin D3 blocks the proliferation and the HH signaling in BCC cells (Bijlsma et al., 2006; Tang et al., 2011). Furthermore, currently there are trials that investigate the topical treatment with vitamin D for the treatment of BCC. Vitamin D supplementation is safe and there exists a vast experience since it has been successfully administered in multiple autoimmune, inflammatory, and infectious diseases. Based on these considerations and the fact that for showing a 20% reduction in the re-development of BCC, the sample size of the trial needs to include 1746 participants with a trial duration of 3 years, the only ethical and feasible design is a phase III clinical trial. Testing this hypothesis in a phase I or II clinical trial would lead to an underpowered trial, with unnecessary exposure of patients to a not optimal trial and wasting financial and personnel resources.

The study design using a control (placebo) arm with triple-blinding and the ITT analysis represent the main strength of the present trial protocol. Genetic profiling (whole-exome-sequencing, vitamin D receptor polymorphism) of the excised tumors for further pathological mechanism analysis represents a further strength of this trial.

Limitations of this study may include those inherent to a multicenter phase III trial, such as recruitment of a big population sample, assuring a proper standardization method for data collection and follow-up of participants across different centers. Thus, a highly developed coordinating center is required for avoiding heterogeneity in clinical practice among centers. Further limitations in the study could be the difficulty in maintaining patients' adherence, as participants would be screened and followed up for an asymptomatic and insidious condition that may take a long follow up period to develop. This may predispose participants to lose adherence to treatment and dropout of the study. Therefore, we intend to strictly comply to the adherence methods stated in our manuscript in order to keep the dropout rate at a minimum.

Author affiliations

1 Dermatological Sciences, Institute of Cellular Medicine, Newcastle University, Framlington Place, Newcastle upon Tyne, NE2 4HH United Kingdom. Ioana.cosgarea@newcastle.ac.uk
2 Esteio Primary Care Centre José Mario de Carvalho (Tamandaré) Rio Grande do Sul, Brazil. ytchemale@gmail.com
3 Hamad Medical Corporation, Doha, Qatar. drhanfuli@hotmail.com
4 Laboratory of Neuromodulation, Department of Physical Medicine and Rehabilitation, Harvard Medical School, Spaulding Rehabilitation Hospital, Boston, MA. mgunduz@neuromodulationlab.org
5 Knowledge Management and Epidemiology Director at CEDIMAT, Danto Domingo, Dominican Republic. Rodriguezjulia05@gmail.com
6 Beth Israel Deaconess Medical Center, Harvard Affiliated Hospital, Boston, Massachusetts mrodri18@bidmc.harvard.edu
7 Centro Universitário Lusíada (UNILUS), Santos, São Paulo, Brazil. leonardolerro@gmail.com

8 Clinica AMO – Assistência Multidisciplinar em Oncologia, Salvador, Bahia, Brazil. andradedeoliveiraju@gmail.com
9 Department of Internal Medicine. School of Veterinary Medicine and Animal Science. University of Sao Paulo Brazil. dschwartz@usp.br
10 Section Neurology, Department of Medicine. Max Rady Faculty of Medicine. University of Manitoba. Health Sciences Centre. Winnipeg Canada and Brandon HSC. Canada. atamayo@pmh-mb.ca
11 Neonatologist, Newborn Care Unit, Blacktown Hospital, NSW, Australia. anjali.dhawan27@gmail.com
12 Essen Medical, Bronx, New York, USA. bel_kismabel_18@hotmail.com
13 Clinica Alemana, FAcultad de Medicina, Universidad del Desarrollo, Santiago, Chile. lschonhaut@almemana.cl ORCID ID https://orcid.org/0000-0003-2150-6054
14 Clínica del Dolor del Bajío, Apaseo el Alto, Gto. Mexico. v.odetteolverah@gmail.com
15 Clínica Reunidas São Victor, Rio de Janeiro, Rio de Janeiro, Brazil talmas.amorim@gmail.com
16 Surgical Oncology Division, Department of Abdominal Surgery, AC Camargo Cancer Center, São Paulo, SP, Brazil. drfelipecoimbra@gmail.com
17 Kidney Transplant Unity, Department of Urology. University of Sao Paulo -Brazil. valmir.filho@hc.fm.usp.br
18 Universidade Estadual de Feira de Santana - UEFS, Department of Health, Collegiate of Medicine. Feira de Santana, Bahia, Brazil. flavioamma@gmail.com.
19 Ophthalmology Department, Hospital Evangelico de Belo Horizonte, AEBMG. Belo Horizonte, MG, Brazil. rguimaraes.paula@gmail.com
20 Department of Medicine III, University Hospital Carl Gustav Carus,Technische Universität Dresden, 01307 Dresden, Germany. Georgiana.Constantinescu@uniklinikum-dresden.de
21 Department of Endocrinology, Grigore T. Popa University of Medicine and Pharmacy, Iasi, Romania

Conflict of interest and financial disclosure

The authors have no personal or financial conflicts of interest to declare.

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