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Desensitization to colecalciferol in 18 patients with immediate hypersensitivity reactions

Özge Atik, MD[a]*, Fatma Merve Tepetam, MD[a], Şeyma Özden, MD[a], Ali Can, MD[b] and Bengü Şaylan, MD[c]

ABSTRACT

Introduction: Hypersensitivity reactions (HSRs) to colecalciferol (vitamin D) have been rarely reported and the mechanism is unknown. As an alternative treatment was not recommended for vitamin D deficiency, a desensitization protocol with colecalciferol can be performed. We found that there is no standard desensitization protocol for vitamin D. In this study, we aimed to investigate clinical features and skin test results of patients with HSRs to the vitamin D and effectiveness of the 6-step desensitization protocol in which we applied oral drops of colecalciferol.

Method: This retrospective cross-sectional study included 18 patients with a history of HSRs to oral vitamin D supplements and patients who were planned to receive oral vitamin D replacement. Before desensitization, some of the patients underwent skin tests (skin prick test and intradermal test) with colecalciferol, and the results were recorded. Skin tests were not performed in patients with a history of drug use (antihistamine, systemic steroid, omalizumab, etc.) that affected the results of skin tests. All patients were applied an one bag 6-step desensitization protocol with colecalciferol. Vitamin D3 solution was administered totally 30 drop (4000 IU)/day (1 drop:133.33 IU of 3333 IU/mL) dose of colecalciferol (Devit-3®, DEVA-Türkiye, 15 mL/50,000 IU, 1 mL = 25 drop) at 15-minutes intervals without premedication.

Results: The patient group consisted of 16 female subjects (89%); the mean age was 46 ± 12 years. When the patients were evaluated in terms of the risk of hypersensitivity reactions according to their clinical history, 5 patients had a history of anaphylaxis with vitamin D preparations (colecalciferol oral drop, n = 3; colecalciferol capsule, n = 2), and 13 patients had a history of HSRs other than anaphylaxis with isolated cutaneous reactions (pruritus, flushing, urticaria and angioedema) (n = 11, colecalciferol oral drop; n = 2, colecalciferol capsule). Skin prick test (SPT) and intradermal test (IDT) were performed on 9 patients. SPTs and IDTs were negative in all patients. Urticaria occur during desensitization in only one patient but vitamin D replacement was performed within the following 48–72 h after HSRs. All other patients tolerated 30 drop (4000 IU) and have continued to take same dose every day for the last 6 weeks with no adverse reactions.

Conclusion: Desensitization with oral vitamin D preparations has a crucial role for patients who can not receive vitamin D supplements by other ways. Vitamin D drop forms, which are better

[a]University of Health Sciences, Süreyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Immunology and Allergy, İstanbul, Turkey
*Corresponding author. University of Health Sciences Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, Allergy and Immunology Clinic Istanbul Turkey. E-mail: drozgeatik@gmail.com
Full list of author information is available at the end of the article

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absorbed than capsule forms which contains the lowest units per/mL without the need to dilute the preparation, not contain any additives with HSRs potential such as gelatin and peanut oil are good option. Our 6-step desensitization protocol with oral drop of colecalciferol is a reliable protocol in patients with a history of vitamin D HSRs.

Keywords: Allergy of colecalciferol, Desensitization, Drug hypersensitivity, Drug reaction

INTRODUCTION

Vitamin D deficiency is a globally public health problem.[1] A significant portion of vitamin D (80–90%) is produced during sun exposure endogenously under the influence of ultraviolet B (UVB) rays is synthesized in the skin. Additionally, there are also small amounts of vitamin D in foods such as fish oil, salmon, mackerel, and tuna. Vitamin D is converted enzymatically in the liver to 25-hydroxyvitamin D (25[OH]D), then in the kidney to 1,25-dihydroxy vitamin D. The half-life of 25-hydroxyvitamin D used to determine a person's vitamin D level is 2 to 3 weeks, while the half-life of the most active form of vitamin D (1,25-dihydroxyvitamin D) is approximately 4 to 6 h. Although there is no consensus on the optimal level, generally 25(OH)D levels above 30 ng/mL (75 nmol/L) are adequate, 20–30 ng/mL (50–75 nmol/L) are insufficient, and levels below 20 ng/mL (50 nmol/L) are deficient is defined as. In addition, a 25(OH)D level <10 ng/mL is defined as a serious is considered a deficiency, 25(OH)D levels below 150 ng/mL; Vitamin D intoxication is mentioned in cases where it is above.[2]

The aim of treatment is to keep serum levels between 30 and 50 ng/mL. Although vitamin D2 (ergocalciferol) and D3 (colecalciferol) derivatives are used, vitamin D3 is preferred to be more effective and to standardise the treatment. In all adults with osteopenia, vitamin D2 or Vitamin D3 4000–6000 IU/day or 50,000 IU/week for 8 weeks, followed by maintenance therapy 1500–2000 IU/day to maintain blood 25(OH)D levels above 30 ng/mL is recommended. In adults with osteoporosis, maintenance therapy of 7000 IU/day for 6–8 weeks is recommended.[3]

Treatment with either vitamin D2 or vitamin D3 is recommended for deficient patients. The intravenous (IV) form of vitamin D (calcitriol) is only recommended in patients with chronic kidney disease undergoing haemodialysis.[4] Oral dosage forms like tablet, capsule and oral solution have different absorption rate. The efficiency of oral absorption of conventional vitamin D3 is approximately 50%.[5] In general, there is more availability for absorption of a drug in oral solutions compared to the capsule and tablet, respectively.[6]

Hypersensitivity reactions (HSRs) to vitamin D (colecalciferol) have been rarely reported in the literature, and these cases are either immediate type HSRs or delayed type HSRs. The severity of immediate type HSRs can range from isolated cutaneous reactions (pruritus, flushing, urticaria, and angioedema) to anaphylaxis due to upper respiratory tract edema (swelling of the tongue and shortness of breath, difficulty in breathing). Delayed type HSRs manifests as synovitis as well as morbiliform eruption.[7–9]

Although it was demonstrated that vitamin D Receptor (VDR), which is expressed in the epithelium, is responsible for extra-skeletal vitamin D (anti-inflammatory, anti-proliferative functions), as well as has a role in immunomodulation,[2,3] the mechanism of HSRs to the vitamin D is unknown. The fact that IgE antibodies to calcitriol were not demonstrated by skin test in any of the reported cases suggests that non-IgE-mediated mechanisms may be responsible. Cholecalciferol undergoes a double hydroxylation in the liver and then in kidney to get the active form of vitamin D is 1,25-dihydroxyvitamin D (1α,25[OH]2D3) [calcitriol], so the active metabolite of vitamin D calcitriol can cause HSRs.[10]

Another hypothesis in the literature on this subject is that the first sensitivity to allergens in the neonatal period is caused by the immunological side effects of vitamin D supplements used to prevent rickets.[11,12] In a case report, the fact that the patient had stereotypic synovitis and morbiliform rash suggested that a type III or IV

hypersensitivity reaction might be responsible.[7] Another important consideration is the suspicion that the reaction is caused by an excipient in the preparation. Gelatin, peanut oil, soya bean oil, and fish derivatives, especially in capsule forms, may be responsible for hypersensitivity reactions.

As an alternative treatment was not recommended for vitamin D deficiency, a desensitization protocol with colecalciferol was performed. In recent years, various desensitization protocols with successful outcomes have been reported in case reports.[7-9] In 1999, Amandeep et al performed successful vitamin D desensitization (intravenous route and subsequently to oral calcitriol administered) in 1 case.[9] Ünal et al[8] performed an 11-step desensitization protocol for oral drop vitamin D in a patient diagnosed with osteoporosis in 2016. In order to ensure that desensitization was specific to colecalciferol rather than an adjuvant, no other protocol was found except for the cautious dosing interval desensitization protocol, which consisted of desensitization with pure colecalciferol rather than a commercial preparation, with desensitization in hospital on the first day and continued at home for the next 6 weeks.

We found that there is no standard desensitization protocol for Vitamin D, in the literature. In this study, we aimed to investigate clinical features and skin tests of patients with HSRs to the vitamin D and effectiveness of the 6-step desensitization protocol in which we administered increasing doses of oral drop colecalciferol (Devit-3® drop 15 mL/50,000 IU). The most important difference of the 6-step desensitization protocol, in which we applied oral drops of colecalciferol in increasing doses in patients with hypersensitivity reactions to the vitamin D, is that it contains the lowest units per/mL without the need to dilute the preparation, does not contain any additives with HSRs potential such as gelatin and peanut oil, and is applied at 15 min intervals without premedication.

MATERIALS AND METHODS

In this retrospective study, 18 patients with a history of immediate hypersensitivity reactions (pruritus, flushing, urticaria, anaphylaxis), which usually developed within the 1-4 h, after the 1-5th dose of vitamin D, and who underwent desensitization with oral vitamin D preparations were included between January 2012 and December 2022 (Table 1). This study protocol was reviewed and approved by [Süreyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital ethics committee], approval number [116.2017.R-307]. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent form was obtained from the patients who participated in the study.

Demographic characteristics such as age, gender, and clinical symptoms were screened from the hospital data system retrospectively. Patients who were planned to receive oral vitamin D replacement, had a medical history of previous peroral vitamin D replacement, and developed hypersensitivity reactions to the vitamin D were analyzed. When atopy of the patients was evaluated, any allergen-specific IgE positivity and/or sensitization on skin prick test (SPT) were taken into consideration.[13,14] Nine patients underwent skin tests (prick and intradermal) with colecalciferol. Skin testing was not performed on patients who had recently used medications that affected skin test results, such as antihistamines, systemic steroids, or omalizumab and whose treatments could not be discontinued. SPT was performed with 1 mg/mL and intradermal testing with colecalciferol at a 1/100 concentration.[8,15] Since most of the patients had osteopenia or osteoporosis at the time of presentation and no alternative drug was available, desensitization was performed without drug provocation testing with the Vitamin D preparation responsible for the immediate type hypersensitivity reactions. Desensitization procedures were carried out in an inpatient setting when comorbid conditions were under control.

Vitamin D3 solution was administered totally 30 drop (4000 IU)/day (1 drop:133.33 IU of 3333 IU/mL) dose of colecalciferol (Devit-3®, DEVA-Türkiye) (15 mL/50,000 IU, 1 mL = 25 drop) at 15 min intervals without premedication. We choose this Vitamin D preparation because in drop form is better absorbed than capsule. forms, has a lower units per mL content without the need for reconstitution, and does not contain additives with potential HSR potential such as gelatin and peanut oil. Moreover, daily applications provide a more suitable option for the continuity of

	Drug	Drug reaction time	Gender	Age	Adverse reaction	Test Result	Presence of Atopy, Additional atopic disease	Additional drug allergy
Patient 1	D-Colefor® capsule	3.th dose 30–40 min	Female	48	Flushing	–	Atopy, Chronic spontaneous urticaria	Vitamin B12
Patient 2	Coledan-D3® drop	1.th dose 45–50 min	Female	67	Pruritus	–	Atopy, Chronic spontaneous urticaria	NSAID
Patient 3	Devit-3 ® drop	1.th dose 30–40 min	Male	60	Urticaria, Angioedema	Negative	Asthma	None
Patient 4	Coledan-D3® drop	1.th dose 5–10 min	Female	66	Hypotension, Syncope, (Anaphylaxis)	–	Atopy	NSAID
Patient 5	Coledan-D3® drop	5.th dose 50–60 min	Female	26	Flushing, Pruritus	Negative	None	Vitamin C
Patient 6	Devit-3 ® drop	5.th dose 30–40 min	Female	50	Angioedema	Negative	Atopy	NSAID
Patient 7	Coledan-D3® drop	3.th dose 20–30 min	Female	36	Flushing, Pruritus	Negative	Atopy	Beta lactam, NSAID
Patient 8	Coledan-D3® drop	2.th dose 40–50 min	Female	26	Flushing	Negative	None	Iron preperations
Patient 9	Coledan-D3® capsule	1.th dose 10–20 min	Female	31	Bronchospasm, urticaria (Anaphylaxis)	Negative	Atopy, Chronic spontaneous urticaria	Beta lactam
Patient 10	D-Colefor® capsule	4.th dose 120–150 min	Female	55	Flushing, Pruritus	Negative	Atopy	NSAID
Patient 11	D-Colefor® capsule	1.th dose 15–20 min	Male	68	Hypotension, bronchospasm, palpitations (Anaphylaxis)	Negative	Atopy	Quinolone
Patient 12	Coledan-D3® drop	1.th dose 15–20 min	Female	46	Hypotension, Palpitations (Anaphylaxis)	Negative	None	Beta lactam
Patient 13	Devit-3 ® drop	3.th dose 180–210 min	Female	52	Pruritus	Negative	None	Iron preperations
Patient 14	Coledan-D3® drop	5.th dose 200–240 min	Female	43	Flushing, Pruritus	–	None	Lansoprazol
Patient 15	Coledan-D3® drop	1.th dose 20–30 min	Female	33	Flushing	–	Chronic spontaneous urticaria	NSAID
Patient 16	Coledan-D3® drop	2.th dose 180–210 min	Female	47	Flushing, Pruritus	–	None	Iron preperations
Patient 17	Devit-3 ® drop	3.th dose 15–20 min	Female	53	Pruritus	–	Atopy	Beta lactam
Patient 18	Devit-3 ® drop	1.th dose 15–20 min	Female	41	Bronchospasm, Palpitations (Anaphylaxis)	–	Atopy, Asthma	Beta lactam, NSAID

Table 1. Basic characteristics of patients, clinical and laboratory findings. *NSAID: Non-steroidal anti-inflammatory drugs min:minutes*

the desensitization process compared to weekly applications.

All patients underwent our self-created 6-step desensitization protocol (Table 2). All patients were observed after desensitization for any HSRs. All patients continued to receive 30 drop (4000 IU) every day for the last 6 weeks and were followed up for 6 weeks for adverse reaction.

Statistical analyses

Statistical evaluation was analyzed using SPSS 21.0 (SPSS Inc., Chicago, IL). Descriptive data were expressed as percentage and mean ± standard deviation according to the distribution. Descriptive statistics for variables were expressed as frequency (%).

RESULTS

A total of 18 patients (16 females, 89%) with a mean age of 46 ± 12 years were included in the study. Osteopenia was the most common indication (n:10) for vitamin D replacement in this study. All patients had a history of HSRs in 1–4 h after using oral vitamin D preparations. The majority were of grade 1 severity (n:13) severity and the remainder of grade 2 (n:2) and grade 3 severity (n:3) according to Brown's grading system.[15] An equal number of patients experienced anaphylaxis to colecalciferol oral drop (3 patients). Only 2 patients reacted to an oral capsule formulation of vitamin D3 (colecalciferol). Seven patients had a story of NSAID allergy, 6 patients had Beta lactam antibiotic HSRs, 6 patients had other drugs (Quinolone, Iron preparations, Vitamin B12, Vitamin C, lansoprazol) HSRs (Table 1). The mean baseline tryptase value was 5.55 ± 1.93 µg/L, mean eosinophil count was 154 ± 115/µL, and total Ig E count was 86.5 ± 84 IU/mL (Table 3). Skin prick test (SPT) and intradermal test (IDT) were performed on 9 patients. SPTs and IDTs were negative in all patients. All patients performed desensitization with Vitamin D preparations without any premedication. Urticaria occurred during desensitization in only 1 patient. Antihistamine treatment was given for her during desensitization and was continued the desensitization. This patient has chronic spontaneous urticaria in addition to drug allergy. Vitamin D replacement was performed within the following 48–72 h after HSRs. All other patients subsequently tolerated 30 drop (4000 IU) and have continued to take 30 drop (4000 IU) every day for the last 6 weeks with no adverse reactions.

Step	Drop	Dose
1	1	133.3 IU
2	2	266.6 IU
3	3	399.9 IU
4	4	533.2 IU
5	7	932.4 IU
6	13	1732.9 IU
Total	30	4000 IU

Table 2. Colecalciferol 6-step desensitization protocol. *(Devit-3®, DEVA-Turkey: 15 mL/50,000 IU; 3333 IU/mL 1 mL = 25 drop, 1 drop = 133.33 IU)*

DISCUSSION

Hypersensitivity reactions associated with vitamin D use are quite rare. Even in cases where HSRs have occurred, it is essential for patients to continue vitamin D supplementation due to concerns like osteopenia and osteoporosis. In these situations, desensitization protocols are implemented; however, the literature reveals a variety of protocols that differ significantly based on factors such as the formulation used (eg, IV, oral capsule, oral drops) and the number of steps involved (some require continued increasing doses in a hospital setting before transitioning to home). In our study, we aimed to present the allergological assessment of 18 patients who experienced immediate type HSRs following vitamin D use, along with the 6-step desensitization protocol we utilized.

The presence of atopy is not a risk factor for drug allergy, although patients with uncontrolled asthma may be more prone to having severe reactions.[16] When analyzing the patients in our study, it was found that 10 of those with a history of vitamin D HSRs were atopic, 4 had a history of chronic urticaria, and 2 had a history of asthma (under control). Additionally, it was noted that all patients, except for 1, had a history of different HSRs particularly to NSAIDs or beta-lactam medications. Our findings suggest that while atopy or related atopic diseases did not influence the

severity of the HSRs observed, the limited sample size should be taken into consideration. In the 3 cases examined in the literature, only 1 patient was observed to have associated atopic conditions such as atopic dermatitis and asthma.[7–9]

When the forms of vitamin D used in the history were questioned, it was learned that 14 patients developed HSRs with natural food additive allergen-free drop forms, 1 patient developed HSRs with Coledan-D3® capsule containing peanut oil and bovine gelatin, and 3 patients developed HSRs with D-Colefor® capsule containing bovine gelatin. However, since the patients had no history of HSRs against foods such as peanut and beef and the skin prick test we performed with these allergens was negative, we excluded the possibility of HSRs against these additives. We could not exclude HSRs due to additives such as antioxidants, oils and dyes contained in different vitamin D preparations mentioned in Table 3.

	n = 18
Age mean ± SD	46 ± 12
Gender female, n (%)	16 (89)
Severity of index reaction, n (%)	
Grade 1[a]	13 (72.2)
Grade 2[b]	2 (11.1)
Grade 3[c]	3 (16.7)
Index vitamin D preparations	
Colecalciferol oral drop	9 (50)
-Coledan-D3® drop **(Additives: Polyoxyl 35 castor oil, sucrose, Citric acid monohydrate, Benzyl alcohol, Tutti frutti flavour, Disodium hydrogen phosphate anhydrous, Pure water)**	
-Devit-3 ® drop **(Additives: Butylhydroxyanisole, sunflower oil)**	5 (27.8)
Colecalciferol oral capsule	3 (16.6)
- D-Colefor® capsule **(Additives: Sunflower oil, vitamin E, edible gelatine (bovine gelatine), purified water, glycerol, sorbitol)**	
-Coledan-D3® capsule **(Additives: Peanut oil, Gelatin (bovine gelatin),Glycerol, Titanium dioxide, Iron oxide yellow, Iron oxide red, Iron oxide black**	1 (5.5)
Indıcations for vitamin D replacement	
Osteopenia	10 (55.5)
Osteoporosis	8 (45.5)
Accompanying drug allergy n (%)	
NSAID	7 (38.9)
Antibiotic	6 (33.3)
Others[d]	6 (33.3)
None	1 (5.5)
Comorbid atopic disease n (%)	
Atopy	10 (55.5)
Urticaria	4 (22.2)
Asthma	2 (11.1)
Baseline tryptase μg/L, mean ± SD	5.55 ± 1.93
Eosinophil/μL, mean ± SD	154 ± 115
Total Ig E IU/mL, mean ± SD	86.5 ± 84

Table 3. Demographic and clinical features of patients. *SD: Standard deviation, BMI: Body mass index, NSAID: Non-steroidal anti-inflammatory drugs; Ig E: Immunoglobulin E. [a]Symptoms of urticaria, angioedema, itching and sudden redness. [b]Symptoms of Bronchospasm, dizziness or gastrointestinal symptoms along with urticaria and angioedema. [c]Including all the above symptoms but also loss of consciousness, hypotension, or hypoxia. [d]Vitamins, proton pump inhibitors, iron preparations*

The mechanism of vitamin D HSRs is not fully known; it is thought that vitamin D is a small steroid-like molecule that is produced endogenously and continuously, with which an adult can mount an IgE-mediated immune response after years of tolerance.[17–19] Immediate-type hypersensitivity reactions (an IgE mediated or a non Ig E mediated pathomechanism) to vitamins are represented by the signs and symptoms include possible cutaneous (pruritus, flushing, urticaria, angioedema), respiratory (dyspnea, wheezing, desaturations, airway tightening), cardiovascular (hypotension, tachycardia, and even cardiovascular collapse), gastrointestinal (nausea, vomiting, diarrhea), and neurologic (syncope, seizure) and anaphylaxis.[20] Of the case reports of HSRs with vitamin D, 2 were reported as immediate type HSRs and 1 as delayed type HSRs and skin prick test and intradermal test results in previous cases were negative like the tests performed in this study.[7–9] This may be due to the low reaction grade of most of our patients. While we lack specific data on vitamin D, it has been reported that the positivity rate of skin prick tests tends to increase with the severity of reactions in patients with a history of HSRs to substances like radiocontrast media.[21] The active metabolite of vitamin D (calcitriol) can cause allergic reactions. In 1999, Amandeep et al reported hypersensitivity to calcitriol, the hormonally active metabolite of vitamin D. In the case with delayed type reaction; sterotypic synovitis and morbiliform rash suggested type 3 or 4 hypersensitivity reactions.[9]

As an alternative treatment was not recommended for vitamin D deficiency, a desensitization protocol with colecalciferol was performed.[22] There is no standard desensitization protocol established for colecalciferol in the literature. Nowadays there are oral drop preparations of vitamin D in different concentrations. Vitamin D intoxication has been reported more frequently in recent years. Vitamin D intoxication (VDI) is usually iatrogenic and is due to the usage of improper doses of vitamin D.[23] Since it is necessary to start desensitization at the lowest dose in drug desensitization, we used the commercial preparation with the lowest concentration (DEVİT-3® drop 15 mL/50,000 IU) in this study as in other studies. In 2016, Unal et al administered 50,000 IU (15 mL) of colecalciferol oral drops in a total of 11 steps at 30-min intervals.[8] In this study, we administered desensitization 4000 IU (30 drops, 1.2 mL) of colecalciferol oral drops in 6 steps at 15-min intervals in 18 patients. The unique aspect of our study is that we administered the daily dose through a desensitization process rather than providing the total dose at once. This method aimed to minimize the risk of adverse reactions while ensuring effective supplementation. It is important that treatment is not interrupted to ensure the continuation of desensitization. In this context, daily applications provide a more suitable option for the continuity of the desensitization process compared to weekly applications.

Our hospital is recognized as one of the leading centers for drug allergy testing in the country. This study presents the largest series of patients with a history of immediate HSRs to different forms of vitamin D. We introduce a practical and straightforward desensitization protocol in this paper. A key distinction of the 6-step protocol using oral drops of colecalciferol– which is more effectively absorbed than capsule forms– is its use of the lowest concentration of units per mL without the need for diluting (fat soluble) the preparation. Furthermore, the formulation excludes common additives that could trigger HSRs such as gelatin and peanut oil. Notably, the desensitization protocol for colecalciferol was completed without premedication. This study has several limitations. Firstly, we were unable to conduct skin tests on patients taking medications (such as antihistamines, omalizumab, and systemic steroids) that could influence the test results. Additionally, patients who did undergo skin testing exhibited negative outcomes. It is important to recognize that a negative skin test may not rule out sensitivity, as it could be related to the metabolite responsible for the reaction. Skin tests are not always a reliable indicator and can create inconsistencies in clinical practice. Furthermore, using the Naranjo scoring system, which considers factors such as time sequence, prior knowledge, withdrawal effects, re-exposure, alternative causes, contributing factors, and investigations, all patients were classified as having a "probable" hypersensitivity reaction to cholecalciferol (with a score of 6–7), while a score of 8 would indicate a definite reaction.[24] According to the guidelines, rapid desensitization is recommended regardless of skin test response in patients whose clinical history suggests an immediate HSRs (IgE mediated or a non-Ig E mediated) for whom no alternative drug

is available.[25–27] Additionally, patients opted for desensitization instead of drug provocation due to the lack of standardized protocols for vitamin D. Many, also rejected provocation testing because of prior reactions to other medications. Given our center's capacity and the urgent needs because of osteopenia and osteoporosis of out-of-town patients, desensitization was the most suitable choice.[28] The final limitation of our study is the absence of a desensitization protocol that initiates with varying concentrations tailored to the severity of the initial reactions. Most of our patients had low reaction index; only 3 patients experiencing a grade 3 reaction. Additionally, it is essential to seek assistance from a pharmacist to obtain a lower concentration of vitamin D, which is not water-soluble and only dissolves in fat.

CONCLUSION

To the best of our knowledge, it is the first study in which desensitization was performed on a high number of 18 patients using a protocol. This research is among the most extensive series investigating hypersensitivity reactions (HSRs) that occur during vitamin D treatment, for which a desensitization protocol is suggested. We present a practical and straightforward desensitization approach in this paper. Further investigations involving a larger patient population are needed to validate the effectiveness of our protocol.

Abbreviations

HSRs, Hypersensitivity reactions; IDT, Intradermal test; NSAID, Non-steroidal anti-inflammatory drugs; SPT, Skin prick test; 25[OH]D, 25-hydroxyvitamin D.

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Data availability

Personal data are kept confidential by the authors within the scope of protection of personal data. Further enquiries can be directed to the corresponding author.

Author contributions

Concept: Ö.A. Ş.Ö.F.M.T. B.Ş, Design: Ö.A. A.C Ş.Ö B.Ş, Data Collection or Processing: Ö.A. F.M.T B.Ş. Ş.Ö, Analysis or Interpretation: Ö.A A.C. Ş.Ö, Literature Search: Ö.A.,B.Ş. A.C, F.M.T, Writing: Ö.A. A.C F.M.T B.Ş.

Author consent

All authors consented for publication.

Statement of ethics

This study protocol was reviewed and approved by Süreyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital ethical comitee, approval number [116.2017.R-307]. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent form was obtained from the patients who participated in the study.

Declaration of competing interest

The authors have no conflicts of interest to declare.

Author details

[a]University of Health Sciences, Süreyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Immunology and Allergy, İstanbul, Turkey. [b]University of Health Sciences, Van Training and Research Hospital, Department of Immunology and Allergy, Van, Turkey. [c]University of Health Sciences Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, Chest Diseases Clinic, Istanbul, Turkey.

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