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EFFECT OF ORAL VITAMIN D SUPPLEMENTATION ON PSORIASIS SEVERITY: DOES IT GENERATE SIGNIFICANT BENEFITS?

EFECTO DE LA SUPLEMENTACIÓN ORAL CON VITAMINA D SOBRE LA GRAVEDAD DE LA PSORIASIS: ¿GENERA BENEFICIOS SIGNIFICATIVOS?

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ABSTRACT

Introduction: Psoriasis is a chronic immune-mediated skin disease with a complex genetic and pathogenic basis, often leading to significant comorbidities and a reduced quality of life. Its prevalence varies globally and exhibits an increasing trend over time. **Methods:** Comorbidities such as psoriatic arthritis, cardiovascular diseases, and mental health issues further compound the burden of psoriasis. Treatment options range from topical therapies to systemic agents, with biologics playing a prominent role in recent years. However, the safety and efficacy of these treatments are continuously assessed through real-world data. Vitamin D has gained attention as a potential therapeutic target due to its role in immune regulation and skin barrier function. **Results:** This review aims to evaluate the efficacy of oral vitamin D supplementation in ameliorating the severity of psoriasis. After bibliographic search, it was found that psoriasis is a multifaceted condition with significant global implications. Biologics have transformed its management, and oral vitamin D supplementation is a promising avenue for further exploration. A comprehensive, patient-centered approach that considers comorbidities and long-term outcomes is crucial for optimizing psoriasis care. **Conclusion:** Further research is needed to fully understand the role of vitamin D in psoriasis and its potential as a therapeutic intervention.

Keywords: Vitamin D, Psoriasis, Severity of Illness Index, Treatment Outcome.(Source: MESH-NLM)

RESUMEN

Introducción: La psoriasis es una enfermedad crónica de la piel mediada por el sistema inmunológico con una base genética y patogénica compleja, que frecuentemente conduce a comorbilidades significativas y una reducción en la calidad de vida. Su prevalencia varía a nivel global y muestra una tendencia creciente con el tiempo. **Métodos:** Comorbilidades como la artritis psoriásica, enfermedades cardiovasculares y problemas de salud mental complican aún más la carga de la psoriasis. Las opciones de tratamiento van desde terapias tópicas hasta agentes sistémicos, siendo los agentes biológicos prominentes en los últimos años. Sin embargo, la seguridad y eficacia de estos tratamientos se evalúan continuamente a través de datos del mundo real. La vitamina D ha llamado la atención como un posible objetivo terapéutico debido a su papel en la regulación inmunológica y la función de barrera de la piel. Esta revisión tiene como objetivo evaluar la eficacia de la suplementación oral de vitamina D en mejorar la gravedad de la psoriasis. **Resultados:** Después de una búsqueda bibliográfica, se encontró que la psoriasis es una condición multifacética con significativas implicaciones globales. Los agentes biológicos han transformado su manejo, y la suplementación oral de vitamina D es un camino prometedor para una mayor exploración. Un enfoque integral centrado en el paciente que tenga en cuenta las comorbilidades y los resultados a largo plazo es crucial para optimizar el cuidado de la psoriasis. **Conclusión:** Se necesita más investigación para comprender completamente el papel de la vitamina D en la psoriasis y su potencial como intervención terapéutica.

Palabras clave: Vitamina D; Psoriasis; Índice de Severidad de la Enfermedad;Terapéutica. (Fuente: DeCS- BIREME)

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INTRODUCTION

Psoriasis is a common, systemic, inflammatory, chronic immune-mediated papulosquamous skin disease that can affect anyone at any age and puts a burden on both the individual and society. It has a complex genetic and pathogenesis architecture, is linked to a number of serious medical disorders, including cardiometabolic syndrome, psoriatic arthritis (PsA), and depression, and has well-described negative effects on patient quality of life (QoL)[1,2]. Psoriasis is predominantly a skin disease that can manifest in various phenotypes, all of them may experience the same symptoms, such as itchiness, burning, and pain. Skin involvement varies in its degree. Reduced serum levels of 25 hydroxyvitamin D (25(OH)D) have been implicated in the pathogenesis of numerous cutaneous conditions, notably including psoriasis. In the extant body of research, investigations into the potential therapeutic effects of oral vitamin D supplementation in the context of psoriasis have only recently gained attention.

Considering the multifaceted influence of vitamin D on diverse cutaneous functions, including immune and inflammation mechanisms, and the pivotal role of its analogues in therapeutic interventions, it is imperative to undertake a rigorous assessment of the efficacy of oral vitamin D supplementation in ameliorating the severity of psoriasis.

Epidemiology

It exerts a substantial global impact, afflicting an estimated 125 million individuals worldwide and affecting approximately 3% of the United States population[3,4]. Its magnitude was underscored by the World Health Organization's declaration in 2014, categorizing it as a "chronic, non-communicable, painful, disfiguring, and disabling disease for which there is no cure" [5]. The annual incidence stands at approximately 80 new cases per 100,000 person-years[6]. However, it is noteworthy that the prevalence of psoriasis exhibits substantial regional variability, ranging from 0.5% in specific parts of Asia to as high as 8% in Norway [6,7]. Psoriasis demonstrates an egalitarian impact, affecting both men and women equivalently, typically manifesting with an onset age averaging 33 years[6].

The ailment encompasses two distinct subtypes characterized by genetic and immunological attributes: early onset, occurring before the age of 40 years (constituting 75% of cases), and early onset, emerging beyond the age of 40 years. Interestingly, the condition may manifest at an earlier age in women, featuring a bimodal onset distribution at the ages of 16 to 22 years and 55 to 60 years[8]. Remarkably, only 19% of countries worldwide possess comprehensive prevalence data on psoriasis, with disparities observed across geographical regions, with higher prevalence among individuals of Caucasian descent [9]. Notably, both prevalence and incidence tend to be lower in children compared to adults [10,11].

Moreover, there is a discernible trend towards an increased prevalence of psoriasis over time. In retrospective cohort studies of adults, the incidence rose from 50.8 cases per 100,000 people between 1970 and 1974 to 100.5 cases per 100,000 people between 1995 and 1999 [12]. Similarly, among children, psoriasis incidence increased from 29.6 to 62.7 instances per 100,000 individuals during the same time frame[10].

The burden of psoriasis extends beyond its physical manifestations, encompassing a significant decrement in the quality of life for most affected individuals and exerting a detrimental influence on their psychosocial well-being. Indeed, avoidance coping mechanisms frequently dominate the lives of psoriasis patients, constituting a prominent daily stressor. This psychological toll is further underscored by the high prevalence of depression, affecting up to 20% of individuals with psoriasis, and the occurrence of suicidal ideation and actions within this population[13].

Regarding vitamin D, it has been observed that individuals afflicted with psoriasis exhibit notably diminished levels of vitamin D compared to control subjects. A statistically significant inverse relationship has been identified between serum vitamin D concentration and key clinical parameters, including disease duration, Psoriasis Area and Severity Index (PASI) score, and erythrocyte sedimentation rate (ESR) levels (p-value <0.001).

Moreover, advanced age and female gender have also been correlated with significantly reduced vitamin D levels in this context [14]. This deficiency has been consistently documented[15-17].

COMORBIDITIES

Psoriatic Arthritis

It represents one of the more prevalent comorbidities associated with psoriasis, afflicting an estimated 0.3–1% of the global population[18]. It has been ascertained that PsA is present in approximately 10-30% of individuals diagnosed with psoriasis [19-21]. This condition exhibits an equal incidence among both genders, with its peak onset typically occurring between the ages of 35 and 45. In most cases where patients with psoriasis subsequently develop PsA, arthritis emerges approximately a decade after the initial onset of their dermatological symptoms. Notably, 15% of individuals experience arthritis prior to the manifestation of cutaneous psoriasis symptoms. It is imperative to note that the severity of joint and skin manifestations in PsA patients does not exhibit a discernible correlation[22].

Moreover, comorbid cardiovascular ailments persist as the predominant causes of mortality in individuals with psoriasis[23]. The prevalence of clinical atherosclerosis, as well as systemic and vascular inflammation, has been linked to psoriasis [24]. Robust, population-based epidemiological investigations have consistently demonstrated that, independent of traditional risk factors such as body mass index (BMI), psoriasis is associated with an elevated risk of cardiovascular events [24]. When controlling for variables such as age, gender, BMI, and established cardiovascular risk factors in comparison to control groups, it becomes evident that individuals with severe psoriasis face an approximately sevenfold increase in the risk of myocardial infarction.

Furthermore, the risk of cardiovascular-related mortality is heightened by 57% in this cohort [25]. Additionally, it is worth noting that individuals with psoriasis exhibit a heightened prevalence of psychosocial distress and psychiatric conditions, including social discomfort, anxiety, and depression[26].

Pathogenesis

The pathogenesis of psoriasis remains intricate and continues to be the subject of ongoing investigation. A hallmark characteristic of psoriasis is the sustained inflammation leading to uncontrolled keratinocyte proliferation and impaired differentiation. This pathophysiological process can be conceptualized as comprising two distinct phases: an initiation phase, potentially triggered by factors such as trauma, infection, or medication; and a subsequent maintenance phase, characterized by a protracted clinical course marked by persistent progression[27,28].

Genetics

A significant genetic basis for psoriasis is observed, as supported by genetic association studies analyzing allele frequencies in affected individuals and controls, as well as the transmission from generation to generation. The importance of genetic factors in the pathogenesis of psoriasis is collectively underscored by these investigations [29,30]. It is noteworthy that more than 70 genes have been identified as being associated with psoriasis; however, it should be emphasized that these genetic variants together represent only 30% of the overall heritability of the condition. This apparent discrepancy can be attributed to several factors, including gene-gene interactions, gene-environment interactions, and the cumulative effects of multiple genetic variations, each of which exerts modest and currently imperceptible individual effects. The genetic locus known as susceptibility 1 to psoriasis (HLA-C; previously referred to as PSORS1), which houses genes within the major histocompatibility complex (MHC), is considered a key feature in the genetic landscape of psoriasis. Approximately 40% of the discernible heritability of psoriasis is represented by the MHC, in conjunction with the minor contributions of numerous other genetic loci[31].

Within the domain of early-onset psoriasis, HLA-C06:02 emerges as the primary genetic risk factor. Interestingly, this allele does not exhibit a discernible association with late-onset psoriasis, PsA, or pustular psoriasis. The inheritance of a single HLA-C06:02 allele elevates the risk of developing psoriasis four to five times [32]. Furthermore, the risk of psoriasis development is substantially amplified by the interaction between HLA-C*06:02 and a risk modifier in the ERAP1 gene, which encodes a critical aminopeptidase involved in antigen processing for HLA class I presentation[33].

Immune system

On the other hand, the initiation and perpetuation of psoriatic inflammation can be attributed to aberrations within the cutaneous innate and adaptive immune responses[27,34]. In particular, the activation of the innate immune system is incited by endogenous danger signals and cytokines.

This activation can coexist with autoinflammatory processes in certain patients and T cell-mediated autoimmune reactions in others. Consequently, psoriasis exhibits a dual character, featuring autoimmune elements underpinning its pathogenesis alongside an inflammatory backdrop[35].

Environmental triggers

Moreover, the manifestation of psoriasis is contingent upon the intricate interplay between genetic predisposition and environmental factors. Environmental triggers encompass a spectrum of influences, including psychological stress, infectious agents, notably streptococcal infections, alcohol consumption, tobacco usage, exposure to pharmacological agents such as lithium and antimalarials, as well as non-steroidal anti-inflammatory drugs. Additionally, in some instances, sunlight exposure has been implicated as a potential triggering factor[8]. Notably, obesity and weight gain serve dual roles, both as risk factors predisposing individuals to the development of psoriasis and as potential catalysts for exacerbating the condition once established[36].

Vitamin D Role in Psoriasis

The role of vitamin D as a main regulator of skin physiology is complex, various functions have been found, among which are the regulation of keratinocytes proliferation, differentiation and apoptosis; regulation of cutaneous immune system (inhibition of T cell proliferation, Tregs induction; down-regulation of pro-inflammatory cytokines; stimulation of antimicrobial peptides expression and regulation of barrier integrity and permeability[37].

In the context of psoriasis, vitamin D plays a crucial role in maintaining the homeostasis of the cutaneous barrier. Numerous investigations have established an association between polymorphisms in the vitamin D receptor (VDR) gene and susceptibility to psoriasis[38]. It has been showing a significant correlation between the A-1012G promoter polymorphism of the VDR gene and psoriasis risk. This association was attributed to reduced VDR mRNA expression, which creates conditions conducive to the disruption of the cutaneous barrier and the development of psoriatic lesions[39].

Furthermore, in psoriatic skin, there is a notable decrease in VDR expression and a concurrent reduction in tight-junction proteins. Tight junctions play a pivotal role in regulating the adhesion and permeability of keratinocytes, as well as in the polarization of cutaneous cell differentiation. They are also involved in regulating extracellular calcium gradients, interact with nuclear and cytoplasmic proteins, and influence the regulation of specific genes implicated in keratinocyte differentiation and proliferation[40]. Despite scientific inquiry, the precise role of vitamin D in the pathogenesis of psoriasis remains unclear.

Clinical Manifestations and Classification

The clinical characteristics of psoriasis exhibit variability contingent upon the specific psoriasis subtype. Psoriasis encompasses a spectrum of distinct variants, including but not limited to plaque psoriasis, guttate psoriasis, erythrodermic psoriasis, and pustular psoriasis. It is noteworthy that individuals may concurrently manifest multiple psoriasis subtypes, even if one subtype typically predominates in a given individual. Across these diverse psoriasis types, a commonality is observed in the form of three core clinical characteristics, namely erythema, epidermal thickness and scaling. Approximately 80% to 90% of all psoriasis symptoms are plaque psoriasis. Sharply defined, erythematous, scaly patches or plaques are the primary symptoms of plaque psoriasis.

While plaque psoriasis can affect any part of the body, the scalp, trunk, gluteal fold, and extensor surfaces like the elbows and knees are frequently afflicted. Large thick plaques and tiny erythematous and scaly papules are both possible lesions in plaque psoriasis. Affected areas are typically clearly defined and frequently symmetrical. New psoriasis lesions may appear at the site of trauma, such as scratching, wounds, or pressure, in the case of the Koebner phenomenon. An Auspitz sign may develop as a result of localized bleeding that happens when the scale is removed from the plaque. Patients with moderate to severe psoriasis or during an exacerbation may suffer significant itching[41].

A plaque's edge extends outward and is the most active part of the plaque, which might cause a central clearance that manifests as lesions with an annular appearance[42].

Plaque psoriasis can affect the skin folds, such as the axillary, inframammary, and vaginal regions, and has a disproportionately negative impact on quality of life when it affects specific areas, such as the face, palms and soles, nails, or intertriginous areas. Intertriginous psoriasis lacks the usual scales found with psoriasis in non-intertriginous areas and can frequently be mistaken for a fungal infection due to the wet skin environment in which it develops. About one-third of people with psoriasis develop genital psoriasis, which is associated with a significantly lower quality of life. Patients who have plaque psoriasis on their palms and soles develop painful, thick, scaly plaques that impair their ability to use their hands and feet normally. Pitting, onycholysis (separation of the nail plate from the nail bed), and dystrophy of fingernails and toenails are all symptoms of psoriasis that can affect the nail apparatus[35].

Other variants

Guttate psoriasis

It accounts for 2% of cases of psoriasis and is distinguished by many 3- to 5-mm pink confetti-like scaly patches. Approximately 66% of newly developed guttate psoriasis cases are preceded by a respiratory illness, such as a streptococcal infection. Most of these instances recover on their own over the course of a few weeks to months, but some do have the potential to become chronic[41].

Erythrodermic psoriasis

Is a rare, serious, and possibly fatal form in which individuals have coalescent erythema, scales, or exfoliation covering at least 75% of the body. Even though it only affects 2% to 3% of people with psoriasis, erythrodermic psoriasis is treated as a dermatological emergency because it can be accompanied by electrolyte problems and potentially fatal desquamation [40,42].

Pustular psoriasis

It can be generalized; it is brought on by conditions including rapid steroid tapering, hypocalcemia, pregnancy, or infection and is linked to a difference in the interleukin 36 receptor antagonist (IL36RN) sequence (formerly a mutation). Pustular forms of psoriasis are uncommon and morphologically distinct, characterized by sterile pustules and erythema. They are divided into three subgroups based on the involved anatomical location: generalized pustular psoriasis (also known as von Zumbusch disease), palmoplantar pustulosis, and acrodermatitis continua of Hallopeau[43].

Diagnosis

An essential step in the diagnostic process involves the systematic exclusion of alternative diagnoses encompassing inflammatory, infectious, and neoplastic disorders, including but not limited to atopic dermatitis, seborrheic dermatitis, pityriasis rosea, syphilis, and cutaneous T-cell lymphoma, in order to establish a comprehensive and accurate diagnosis. For instance, the clinical presentation of atopic dermatitis may bear a resemblance to that of plaque psoriasis, featuring pruritic erythematous patches and plaques with associated scaling. However, it is crucial to discern that, in contrast to plaque psoriasis, lesions in atopic dermatitis tend to exhibit a higher propensity for pruritus and do not typically display the distinctive well-defined margins characteristic of psoriatic lesions[41].

Clinic approach

Patients presenting with clinical suspicion of chronic plaque psoriasis should undergo a comprehensive dermatological evaluation, encompassing a meticulous examination of various anatomical sites, including the scalp, nails, and anogenital region. Within this diagnostic context, the presence of chronic inflammatory plaques characterized by well-defined borders and marked scaling constitutes significant supportive evidence, particularly when these manifestations extend to areas such as the scalp, ears, elbows, knees, and the umbilicus. In instances where diagnostic certainty is elusive, the identification of concomitant nail involvement or the presence of inverse psoriasis in anatomical regions such as the intergluteal cleft can provide valuable diagnostic support for the confirmation of a psoriasis diagnosis.

Skin biopsy

In cases where diagnostic ambiguity persists despite a thorough review of the patient's medical history and physical examination, the implementation of a skin biopsy may be warranted. Typically, a 4 mm punch biopsy of the affected skin area is performed, although a shave biopsy through the mid-dermis may also suffice in certain instances. To differentiate between psoriasis and superficial fungal infections, such as dermatophytosis, a histological assessment of the biopsy samples can be facilitated using the periodic acid-Schiff-diastase (PAS-D) staining technique. This method aids in the characterization and differentiation of the underlying pathological processes, contributing to a more precise diagnostic determination.

Assess comorbid conditions

In addition to the evaluation above, patients with psoriasis should be assessed for signs or symptoms of PsA and other comorbidities[44]. In pursuit of timely detection, it is recommended to implement routine screening for signs and symptoms of PsA, as stipulated by joint guidelines established by the American Academy of Dermatology and the National Psoriasis Foundation[44]. Such screening practices encompass the inclusion of specific inquiries aimed at identifying potential indicators of PsA, including but not limited to questioning patients about the presence of joint pain, morning joint stiffness, and any manifestations of back discomfort, even if patients may not readily recognize the latter as indicative of joint-related concerns.

Treatment

Psoriasis, characterized by a chronic and relapsing course, typically necessitates prolonged therapeutic interventions. The selection of an appropriate treatment strategy for psoriasis is contingent upon a multitude of factors. In this review, we will commence by general principles and key considerations. Subsequently the conventional therapeutic modalities including topical, phototherapy, systemic treatments, before delving into emerging and innovative approaches, specifically focusing on biologics.

General principles

Comorbid conditions

First of all, the presence of comorbid conditions plays a pivotal role in therapeutic decision-making. In patients concurrently afflicted with PsA, the preferred therapeutic modalities encompass systemic agents such as methotrexate or biologics, designed to target both cutaneous and articular manifestations. Additionally, the choice of therapeutic agents is significantly influenced by the presence of concurrent medical conditions, including but not limited to HIV, hepatitis B or C infections, alcoholism, cardiovascular disease, or a history of malignancy[45]. Consequently, a holistic approach to treatment is essential, encompassing lifestyle interventions that prioritize smoking cessation, decreased alcohol consumption, weight reduction, enhanced sleep quality, and regular exercise, all of which are regarded as pivotal components of comprehensive care. Furthermore, age emerges as another vital determinant in the therapeutic selection process. It is imperative to consider age-related pharmacokinetic variations, such as the reduced efficiency of drug excretion observed in elderly patients, particularly in the case of treatments like methotrexate. Additionally, certain therapeutic agents, such as acitretin, raise concerns related to teratogenic effects, rendering them unsafe for administration in children or women of childbearing age who aspire to conceive[45].

Clinical practice guidelines

Recent management guidelines with useful treatment algorithms exist in the United States[46] and Europe[47]. Clinical assessment of disease severity and treatment response can be quantified using various scoring systems. Among these, the PASI score stands out as a widely employed metric, particularly in the context of clinical trials, especially those focused on the development and evaluation of biologic therapies. In a general clinical context, mild to moderate cases of psoriasis typically lend themselves to topical management strategies, which may involve the combined utilization of glucocorticoids, vitamin D analogues, and phototherapy. Conversely, the management of moderate to severe psoriasis often necessitates a transition to systemic treatment modalities for effective control of the condition.

The characterization of moderate-to-severe plaque psoriasis exhibits variability on a global scale. In several European nations, this categorization relies on diverse parameters. These parameters encompass psoriasis coverage exceeding 10% of the BSA, a PASI score equal to or exceeding 10, or an assessment of the detriment to the individual's quality of life via a Dermatology Life Quality Index (DLQI) score surpassing[10]. Alternatively, the definition of moderate-to-severe psoriasis may also encompass the presence of one or a combination of the following factors: a significant impact of the disease on physical, social, and psychological well-being, leading to conditions such as depression or anxiety, or localized psoriasis that eludes control with topical therapies and is accompanied by functional impairment or substantial distress[48].

An alternative guideline underscores the classification of patients into two categories: those deemed appropriate for topical therapy and those deemed suitable for systemic therapy. Patients falling into the category suitable for systemic therapy are characterized by meeting at least one of three defined criteria: psoriasis involvement of more than 10% of their BSA, the presence of psoriasis at specialized anatomical sites (including the scalp, face, palms and soles, or genitalia), or a lack of therapeutic response to topical interventions. In certain regions, clinical practice guidelines for moderate-to-severe plaque psoriasis have transitioned away from the sequential approach known as "step therapy" (commencing with phototherapy, followed by oral agents, and subsequently biologics) towards a concurrent consideration of treatment options, including biologics, oral agents, or phototherapy[49].

Topical therapy

Patients derive significant advantages from the application of emollients. In cases where psoriatic involvement is confined to a limited anatomical area, typically comprising less than 3–5% of the total body surface, the cornerstone of therapeutic intervention revolves around the utilization of topical agents. This therapeutic armamentarium encompasses corticosteroids, vitamin D3 analogues, calcineurin inhibitors, keratolytics, and combination topical agents, for example, the combination of corticosteroids with vitamin D3 analogues. These agents are available in various pharmaceutical vehicles such as creams, ointments, foams, or gels[50].

Vitamin D analogs

In recent decades, it has been demonstrated the skin's significant role as a target tissue for 1,25-dihydroxyvitamin D3 (51,52). Numerous topical vitamin D analogues, including but not limited to calcitriol, calcipotriene, tacalcitol, and maxacalcitol, have garnered approval for the treatment of psoriasis. These agents are employed either as standalone therapies or in conjunction with corticosteroids. Their mechanism of action primarily involves immune modulation and the restoration of normal keratinocyte maturation.

Until 2009, calcipotriene constituted the sole topical vitamin D analog accessible within the United States. Calcipotriene is formulated in various preparations such as cream, solution, ointment, foam, or in combination with betamethasone dipropionate as an ointment, suspension, or foam. The topical application of calcitriol ointment has been a longstanding practice in Europe and has since become accessible in the United States. In comparative assessments with calcipotriene, calcitriol demonstrates a propensity to provoke less dermal irritation, particularly in sensitive anatomical regions, such as skin folds[53].

Calcipotriene

Calcipotriene (also known as calcipotriol) is a well-established therapeutic agent for the treatment of psoriasis. While the exact mechanistic intricacies are yet to be fully elucidated, a pivotal pharmacological attribute is its profound hypoproliferative influence on keratinocytes[54].

Calcitriol

The mechanism of action attributed to calcitriol shares similarities with that of calcipotriene, primarily involving the drug's capacity to impede keratinocyte proliferation and promote keratinocyte differentiation. Furthermore, calcitriol exerts inhibitory effects on T cell proliferation and various inflammatory mediators[55]. In a comprehensive systematic review, the comparative effectiveness of calcipotriene and calcitriol was found to be equivalent. Nevertheless, in anatomically sensitive or intertriginous regions of the integument, calcitriol demonstrates a propensity for lower irritant potential in comparison to calcipotriene[56].

It is noteworthy that while these vitamin D analogues exhibit a somewhat lower efficacy when compared to corticosteroids, they are characterized by a more favorable adverse-effect profile [55].

Phototherapy

In cases involving patients afflicted by moderate-to-severe psoriasis, often characterized by involvement of greater than 10% of the BSA and the absence of PsA, phototherapy emerges as a viable therapeutic alternative, particularly when the practicality of applying topical treatments to extensive areas becomes challenging. Phototherapy harnesses the immunosuppressive potential of ultraviolet (UV) radiation, which exerts localized effects on the pathogenesis of psoriasis. These effects encompass the direct impact on Langerhans' cells, inhibition of epidermal hyperproliferation and angiogenesis, and the induction of selective apoptosis in cutaneous T cells, thus contributing to the amelioration of psoriatic manifestations[57].

Systemic therapy

In the management of patients with moderate-to-severe psoriasis, denoted by involvement of greater than 10% of the BSA, treatment options encompass both phototherapy and systemic therapy, the latter being available in oral or injectable forms. It is noteworthy, however, that patients frequently exhibit a preference for systemic therapy over phototherapy. Moreover, systemic therapy may be deemed appropriate for individuals with psoriasis affecting less than 10% of BSA, particularly when it encompasses anatomical regions of significant functional importance or aesthetic concern, such as the face, scalp, palms, or soles. Additionally, systemic therapy may be warranted in cases where concomitant PsA coexists, further emphasizing its relevance in a broader clinical context[46].

Prior to the emergence of biologics, oral systemic therapies held a longstanding position as the primary therapeutic modality for the management of moderate-to-severe plaque psoriasis. These orally administered small molecules exert their pharmacological effects by interacting with widespread intracellular targets, thus affording a relatively broader spectrum of action when compared to biologics. Among the frequently employed oral agents in the treatment of psoriasis are methotrexate, ciclosporin, acitretin, fumarates, and apremilast[53]. Administered orally or intramuscularly, methotrexate is the oldest systemic therapy for psoriasis and is widely used owing to its low cost[58].

Biologics

The contemporary usage of the term "biologics" encompasses intricate engineered molecules, including monoclonal antibodies and receptor fusion proteins. Notably, biologics distinguish themselves from the systemic therapies mentioned earlier by their

distinct mode of action, wherein they selectively target specific inflammatory pathways. Furthermore, the administration of biologics predominantly involves subcutaneous injection, although intravenous (i.e., infliximab) administration may also be implemented, often following diverse weekly dosing schedules[45].

In clinical practice, the initiation of biologic therapy should be regarded as a primary therapeutic approach for cases of moderate-to-severe psoriasis, particularly when the condition profoundly impacts the patient's QoL or when concurrent PsA is present. Additionally, consideration of biologics is warranted in other instances of moderate-to-severe psoriasis, such as when traditional systemic therapies prove ineffective in achieving disease control or when patients experience intolerance to traditional systemic therapies due to adverse effects[45]. Over the past two decades, the landscape of psoriasis and PsA treatment has undergone a profound transformation, primarily attributable to the advent of biologics. In this context, the main therapeutic agents are primarily comprised of recombinant monoclonal antibodies or receptor fusion proteins, which include a range of humanization levels, such as fully human, humanized, or human-mouse chimeric entities. Their mechanism of action is predicated on the precise targeting of specific inflammatory mediators implicated in the pathogenesis of these conditions.

Notably, with the exception of infliximab, the administration of biologics for psoriasis is accomplished through subcutaneous injection. Presently, there are eleven biologics classified into four distinct categories: anti-TNFα agents, anti-IL17 agents, anti-IL-12p40 or IL-23p40 inhibitors, and anti-IL-23p19 inhibitors, all of which are currently employed for the treatment of moderate-to-severe psoriasis. Specifically, there are four anti-TNFα agents utilized in the management of psoriasis, namely adalimumab, certolizumab pegol, etanercept, and infliximab. Additionally, three anti-IL-17 agents have garnered approval for this purpose, comprising secukinumab, ixekizumab, and brodalumab[41]. The authentic assessment of the safety profile of biologics for psoriasis, and to a somewhat lesser extent, their efficacy, necessitates recourse to real-world evidence, primarily furnished through the sustained vigilance of long-term pharmacovigilance registries. Notable examples of such registries encompass the British Association of Dermatologists Biologics and Immunomodulators Register in the United Kingdom, PsoBest in Germany, and BIOBADADERM in Spain[59-61]. These comprehensive databases are instrumental in providing valuable insights into the practical and extended-term outcomes associated with the utilization of biologic therapies in the real-world clinical context. The currently available data offer a reassuring perspective regarding the overall safety profile of biologics, with no substantial indications of heightened risks pertaining to infections or malignancies, provided that requisite pretreatment assessments and annual screening protocols are diligently adhered to.

Vitamin D Supplementation and Psoriasis Severity

Vitamin D represents a pivotal pro-hormone with pleiotropic effects, which can be elucidated by the widespread distribution of vitamin D receptors throughout the human body. These receptors find expression in various cell types, including keratinocytes, dendritic cells, macrophages, and T cells. In addition to its widely recognized function in the regulation of calcium homeostasis, vitamin D assumes significant roles in mitigating inflammatory responses, harmonizing innate and adaptive immune processes, and preserving the integrity of the cutaneous barrier. This multifaceted functionality is further underscored by its influence on keratinocyte maturation[62].

For these aforementioned reasons, the diminishment of 25(OH)D levels may assume a pivotal role in the pathogenesis of psoriasis. This reduction potentially contributes to the establishment of a pro-inflammatory

milieu and the activation of immune responses, leading to various localized consequences, which encompass impacts on the cutaneous barrier and keratinocyte function, ultimately culminating in the development of psoriatic lesions[64].

Lower serum 25(OH)D levels have been associated with the pathogenesis of several skin disorders, such as atopic dermatitis, vitiligo, alopecia areata, and also psoriasis[65-67]. Indeed, vitamin D is recognized for its influence on various skin functions, encompassing the regulation of keratinocyte proliferation, differentiation, and apoptosis. Consequently, perturbations in vitamin D metabolism hold the potential to assume a central role in the pathogenesis of psoriasis[68].

One of the most widely recognized therapeutic approaches for the management of psoriasis involves the prescription of vitamin D analogs, which may be employed either as standalone agents or in combination with corticosteroids[68,69]. Their efficacy could be ascribed to the inhibition of keratinocyte proliferation and induction of keratinocyte differentiation[70]. Nevertheless, in light of the existing body of evidence, the effectiveness of oral vitamin D supplements in the context of psoriasis treatment remains a matter of uncertainty. A case-control study, structured to assess serum 25(OH)D levels in individuals afflicted by psoriasis compared to healthy controls, aimed at elucidating potential clinical associations. The study discerned that a deficiency in 25(OH)D is prevalent among those with severe forms of psoriasis. Furthermore, the findings propose that maintaining serum 25(OH)D concentrations above the threshold of 30 ng/ml could potentially confer benefits in terms of disease progression, particularly in the context of autoimmune and inflammatory conditions like psoriasis[71]. Recent findings have indicated that individuals with psoriasis exhibiting insufficient (21-29 ng/mL) or inadequate (<20 ng/mL) levels of vitamin D are at a heightened susceptibility to experiencing exacerbation of the condition following vaccination. It has also been noted that vaccination during the summer months, characterized by heightened photo-exposure, may serve as a protective factor in this context[72].

There are open label studies indicating that oral vitamin D interventions can enhance PASI score[56,73]. One clinical trial demonstrated that oral vitamin D supplementation exhibited superior efficacy compared to a placebo in terms of ameliorating the PASI score after a 3-month intervention period. However, it is noteworthy that this observed effect dissipated upon longer-term follow-up, extending to 6 months[74].

An umbrella review regarding the utilization of oral vitamin D in the treatment of individuals afflicted with psoriasis revealed a notable disparity between its long-established use as a topical therapeutic agent in managing psoriasis and the relatively recent exploration of systemic vitamin D administration for this purpose. Within the realm of existing literature reviews, only recently have studies examined systemic vitamin D administration in psoriasis. Remarkably, spanning the timeframe from 1985 to the present, only a limited number of studies have undertaken an assessment of the efficacy of oral vitamin D in individuals with psoriasis. Consequently, the outcome of these reviews proved to be both inadequate and inconclusive. It is worth noting that the majority of studies did not report any adverse effects associated with doses falling within a relatively narrow range, typically spanning from 0.25 to 2 µg/day. Conversely, there exists a dearth of evidence concerning the efficacy and potential adverse outcomes associated with the highest doses of systemic vitamin D in the context of psoriasis management[75].

Considering the currently available high-quality evidence, a systematic review and meta-analysis addressing the efficacy of oral vitamin D supplementation in ameliorating disease severity among individuals afflicted with psoriasis. The study scrutiny of 5018 articles, ultimately culminating in the inclusion of four studies for qualitative evaluation, and three studies for quantitative analysis. The findings revealed that vitamin D supplementation exhibited efficacy in diminishing the PASI score following a 6-month intervention period (mean difference [MD] = -

0.92, 95% confidence interval [CI] = -1.72 to -0.11). However, subsequent to the application of Hartung-Knapp adjustment, the observed results failed to attain statistical significance (MD = -0.92, 95% CI = -2.21 to 0.38). Consequently, the effectiveness of vitamin D supplementation could not be definitively ascertained, prompting the suggestion that more randomized controlled trials featuring larger sample sizes are imperative to yield robust and conclusive outcomes [76].

Another systematic review and meta-analysis assessed the association between hypovitaminosis D in individuals with psoriasis and the effectiveness of vitamin D supplementation in inducing remission of psoriatic symptoms, as assessed through the PASI. A total of 27 articles were included in the statistical analysis. The results of this analysis revealed that patients diagnosed with psoriasis exhibited significantly lower levels of 25(OH)D in comparison to healthy controls.

Despite the substantial degree of data heterogeneity, the findings demonstrated a statistically significant difference of -6.26 (95% CI: -8.60, -3.92) ng/dL between the two groups (21.0 ± 8.3 vs. 27.3 ± 9.8, $p < 0.00001$). These outcomes were consistent with those reported in a prior systematic review and meta-analysis, which similarly underscored a noteworthy correlation between diminished 25(OH)D levels and the presence of psoriasis [77].

Starting with an initial pool of 107 articles, Pituweerakul et al. undertook a meticulous selection process, ultimately identifying ten prospective cohort studies comprising over 6200 control subjects and nearly 700 cases. These studies collectively demonstrated a substantial reduction in serum vitamin D concentrations among individuals afflicted by psoriatic disease [78]. Nonetheless, a definitive determination regarding whether diminished 25(OH)D levels represent a consequence of psoriasis or potentially act as a contributing factor remains elusive. Intriguingly, despite the historical administration of vitamin D therapy to psoriasis patients over several years, supplementation did not yield a statistically significant improvement in the PASI score. This observation suggests that additional factors may be intricately involved in the absorption of vitamin D, thereby warranting consideration of supplementation strategies aimed at augmenting 25(OH)D serum levels in individuals grappling with chronic conditions such as psoriasis [77].

CONCLUSIONS

Psoriasis is a complex multifactorial disease for which various novel therapies have arisen in the past years. Despite the refinement of the targeted therapies, psoriasis remains a treatable but so far not curable disease. Clearly, more research is required to answer the question of why the drug survival of some biologics is limited. Further studies are needed to clarify the causal relationship between hypovitaminosis D and psoriasis and to determine the efficacy of vitamin D supplementation in patients affected by psoriasis, specifying optimal dosage, possible supplements combinations, any adverse events, and other factors involved. Large randomized controlled trials must be done to see whether increase in 25(OH)D levels would result in a statistically significant clinical improvement. A favorable effect of oral vitamin D supplementation in patients with psoriasis could not be verified, however more randomized controlled trials are required to produce robust results and definite conclusions.

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