ACIN
ASOCIACIÓN COLOMBIANA DE INFECTOLOGÍA

infectio

REVIEW

Seborrheic dermatitis and its relationship with *Malassezia spp*

Manuel Alejandro Salamanca-Córdoba[†,1,2], Carolina Alexandra Zambrano-Pérez[2,3], Carlos Mejía-Arbeláez[2,4], Adriana Motta[5], Pedro Jiménez[6], Silvia Restrepo-Restrepo[7], Adriana Marcela Celis-Ramírez[1,8]*

Abstract

Seborrheic dermatitis (SD) is a chronic inflammatory disease that that is difficult to manage and with a high impact on the individual's quality of life. Besides, it is a multifactorial entity that typically occurs as an inflammatory response to *Malassezia* species, along with specific triggers that contribute to its pathophysiology. Since the primary underlying pathogenic mechanisms include *Malassezia* proliferation and skin inflammation, the most common treatment includes topical antifungal keratolytics and anti-inflammatory agents. However, the consequences of eliminating the yeast population from the skin, the resistance profiles of *Malassezia* spp. and the effectivity among different groups of medications are unknown. Thus, in this review, we summarize the current knowledge on the disease´s pathophysiology and the role of *Malassezia* sp. on it, as well as, the different antifungal treatment alternatives, including topical and oral treatment in the management of SD.

Key words: seborrheic dermatitis, *Malassezia*, pathogenic role, treatment.

Dermatitis seborreica y su relación con *Malassezia spp*

Resumen

La dermatitis seborreica (DS) es una enfermedad inflamatoria crónica, con un elevado impacto en la calidad de vida del individuo. Además, DS es una entidad multifactorial que ocurre como respuesta inflamatoria a las levaduras del género *Malassezia* spp., junto con factores desencadenantes que contribuyen a la fisiopatología de la enfermedad. Dado que el mecanismo patogénico principal involucra la proliferación e inflamación generada por *Malassezia* spp., el tratamiento más usado son los agentes tópicos antifúngicos y antiinflamatorios. Sin embargo, se desconocen las consecuencias de eliminar la población de levaduras de la piel, los perfiles de resistencia de *Malassezia* spp. y la efectividad entre grupos diferentes de medicamentos. Por tanto, en esta revisión de la literatura, resumimos el conocimiento actual sobre la fisiopatología de la enfermedad y el papel de *Malassezia* sp., así como de las diferentes alternativas de tratamiento antifúngico tanto tópico como oral en el manejo de la DS.

Palabras claves: Dermatitis seborréica, *Malassezia*, tratamiento

Introduction

Seborrheic dermatitis (SD) is a chronic and recurrent inflammatory skin condition with a preference for areas rich in sebaceous glands[1]. The disease is characterized by poorly defined scales and erythematous plaques, with high variability in amplitude and morphology, depending on the location of the lesions[2]. Areas as the scalp, facial region, especially nasolabial folds and lines and the supraciliary region, external auditory canals, anterior auricular areas, and genitalia are affected. Itching is a symptom referred by 80% of patients, especially those whose scalp is affected[3]. Dandruff is refered to a mild condition of SD, characterized by itchy, flanking skin without inflammation[1].

According to the age group, four principal variants of SD are recognized: SD in adults, infants, SD associated with HIV (Human Immunodeficiency Virus) and seborrhea type dermatitis associated with medications[4]. On the other hand, the spectrum of the clinical variants in adults include blepharitis,

† Deceased
1 Grupo de Investigación Celular y Molecular de Microorganismos Patógenos (CeMoP), Department of Biological Sciences, Universidad de los Andes, Bogotá, Cundinamarca, Colombia
2 School of Medicine, Universidad de los Andes, Bogotá, Cundinamarca, Colombia
3 https://orcid.org/0000-0002-5158-7580
4 https://orcid.org/0000-0003-1294-7288
5 Universidad el Bosque. Bogotá, Cundinamarca, Colombia. https://orcid.org/0000-0002-1924-1256
6 Laboratorio de Fitopatología, Facultad de Ciencias Básicas y Aplicadas. Universidad Militar Nueva Granada. Cajicá, Cundinamarca, Colombia. https://orcid.org/0000-0003-1032-292X
7 Laboratorio de Micología y Fitopatología (LAMFU), Chemical and Food Engineering Department, Universidad de los Andes, Bogotá, Cundinamarca, Colombia. https://orcid.org/0000-0001-9016-1040
8 https://orcid.org/0000-0003-3057-1966
* Autor para correspondencia.
Correo electrónico: acelis@uniandes.edu.co

Recibido: 04/08/2020; Aceptado: 26/09/2020

Cómo citar este artículo: M.A. Salamanca-Córdoba, *et al.* Seborrheic dermatitis and its relationship with *Malassezia spp.* Infectio 2021; 25(2): 120-129
http://dx.doi.org/10.22354/in.v25i2.930

exfoliative dermatitis, pityriasiform SD, flexural SD, folliculitis and pityriasis capitis. In the infant, the variants include SD of the scalp, Leiner's disease and pityriasis amiantacea. Even though, *Malassezia* spp. role in the pathogenesis of seborrheic dermatitis remains controversial, fungal eradication showed a strong association with the remission of the clinical presentation[5]. Therefor host and yeast factors involved in the transition of *Malassezia* from commensal to pathogen are matter of studies. Besides, consequences of removing the yeast population from the skin, the resistance profiles of *Malassezia* spp. and the side effects on different groups of medications are little known. Here, we are presenting a revision of the pathophysiology of SD, the role of *Malassezia spp*. and alternatives for both topical and oral antifungal treatment in the management of the disease.

Materials and methods

A bibliographic search of review articles or management guidelines was carried out between December 1, 2018, and May 31, 2019, in the databases: MEDLINE-PUBMED, EMBASE, and SCOPUS, as follows: Title or type of publication: Review OR update. Title/Abstract: «dermatitis, seborrheic» [MeSH Terms] AND treatment [MeSH Term] AND guidelines [MeSH Terms]. We only included papers in English. The articles found were evaluated in terms of their content, feasibility, completeness, consistency, and the quality of the evidence.

The disease and *Malassezia*

The etiology of the disease is multifactorial and it is associated with the presence of *Malassezia* yeast, hormonal factors, levels of sebum secretion, immune response, neurogenic factors, and external factors. The three main etiological factors correlated to incidence of SD are: presence of *Malassezia spp*., sebaceous secretion and the individual susceptibility to develop the pathology[6]. Immune system plays an essential role in develop of symptoms, being asymptomatic in immunocompetent individuals[7].

Malassezia species appear to contribute by triggering the skin innate immunity through complex interactions between fungal cells and virulence factors. This ends up in increasing the production of lipases, inducing an inflammatory response by releasing oleic acid and arachidonic acid, and producing bioactive components from sebum lipids[8]. Released unsaturated fatty acids and metabolites have direct irritant and scaling effects on keratinocytes, while triggering an increased inflammatory response secondary to loss of the epidermal barrier function. Also, the arachidonic acid, metabolized by cyclooxygenase, serves as a source of pro-inflammatory eicosanoids, as well as prostaglandins, which contribute to the damage in the corneum stratum. Simultaneously, the keratinocytes produce pro-inflammatory cytokines, IL-1α, IL-6, IL-8, and TNF-α, which increase and maintain the inflammatory response, thus establishing the chronicity of the infection [9].

Epidemiology

Prevalence of SD is highly variable, between 3 to 10% of the general population, and it is more frequent in men than in women[5]. Some studies reported a high incidence in adolescents, reaching up to 11%[10]. Other studies estimate that this condition affects between 2 and 5% of the population, with no racial bias[9]. Regarding the age of presentation, a higher frequency of cases has been demonstrated in children, especially among those younger than three months, with the cradle cap presentation, affecting from 11.6% to 70.0% in some cohorts, and also in adults between 30 and 60 years old, with an epidemiological peak between the third and fourth decade of life[11].

The main host's risk factors described are the genetic predisposition, hyperhidrosis, malnutrition, immune deficiencies, using systemic corticosteroids and contraceptives, as well as environmental conditions such as high temperature, humidity, and the ocurrence of dysbiosis processes of the microbiota, especially of the genera *Cutibacterium* (*Propionibacterium*)[12], *Staphylococcus* and *Malassezia*[13].

SD is one of the most common dermatoses in individuals infected with HIV, especially those with a CD4 T lymphocyte count below 400 cells/mm[3,14]. In Colombia, Rincón et al. reported the isolation of *Malassezia spp*. from lesions of patients with different dermatological entities, *M. globosa* was the predominant species in HIV-positive SD patients[15]. In subsequent studies on HIV-positive SD patients, the predominant species were *M. restricta* and *M. furfur*, whereas in patients HIV-negative was *M. sympodialis*[16].

Other medical conditions associated with an increased incidence of SD are parkinsonism, neuroleptic-induced Parkinson-plus, familial amyloidosis, Down's syndrome, and patients with psychiatric conditions being treated with haloperidol, lithium, buspirone, and chlorpromazine[9].

Malassezia and its pathogenicity

The yeast of the *Malassezia* genus (formerly called *Pityrosporum*) belongs to the phylum Basidiomycota, sub-phylum Ustilaginomycotina, class *Malasseziomycetes*[17]. It is characterized to be lipid-dependent and lipophilic and for being capable of metabolizing the fatty components of sebum[18]. This last ability influences its preferencial distribution on body areas rich in sebaceous glands. *Malassezia* has been recognized, for more than a century, as a normal resident of the humans skin microbiota but, in recent times, also as a potential pathogen, because it is isolated from the skin in individuals affected by SD, as well as for the therapeutic response to the use of antifungals[19].

The *Malassezia* genus has been subject to multiple taxonomic reviews. However, in recent decades, the introduction of molecular techniques has allowed to describe the presence of at

least 18 species[17,18](Table 1). Two especies, *Malassezia restricta* and *M. globosa,* are considered the most important species in the development of SD. However, some studies have also involved *M. furfur, M. sympodalis, M. obtusa* and *M. slooffiae* [20,21].

Due to the lipid requirements of this yeast, their identification and characterization can be performed using phenotypic characteristics such as the production of catalase and β-glucosidase, as well as with lipid assimilation profiles (Tween)[22]. Genotypic characteristics based on the sequencing of ribosomal RNA subunits (rRNA) is the *gold standard* for their identification[17]. However, these techniques are not conducted in the routine diagnosis.

There are different hypotheses regarding the pathophysiological mechanisms of *Malassezia* causing disease [22]. *Malassezia* yeast is found mainly in the infundibulum of the sebaceous glands, where the freely available lipids constitute their primary source of energy. On the skin, *Malassezia* can establish two kind of relationships with its host. The first is a commensalism, where the yeasts and the skin are in a state of equilibrium, and the yeast is managing to evade the local immune response. The second is a pathogenic relationship, where *Malassezia* proliferate without producing inflammation, as happens in pityriasis versicolor, or it can increase widely and produce swelling, as in the cases of SD, atopic dermatitis, and psoriasis [23].

In an inflammation scenario, *Malassezia* can generate the process associated with its overgrowth by three main mechanisms. First, causing evident damage to the epidermal barrier through the production of lipases and phospholipases. On a healthy skin, this yeast uses the essential nutrients for its growth without causing disease. However, when the epidermal barrier is disturbed, the yeast adapts and modifies the expression of enzymes involved in the acquisition of energy, such as lipases and phospholipases. At the same time, they synthesize bioactive indols (ligands) that act on the aryl-hydrocarbon (AhR) receptor, expressed in most of the epidermic cells [24].

Table 1. Taxonomic classification of the genus *Malassezia*

Malassezia species	Reference
*M. globosa**	Microbiota of human skin[17,18] Important agents in the development of SD [17, 20]
*M. restricta**	
*M. sympodialis**	
*M. furfur **	
M. yamatoensis	
M. arunalokei sp. Nov	
*M. obtusa **	
*M. slooffiae**	
M. dermatis	
M. japonica	
M. pachydermatis	Colonize the skin of animals [21]
M. nana	
M. caprae	
M. equina	
M. cuniculi	
M. brasiliensis sp. Nov	
M. psittaci sp. Nov	
M. vespertilionis sp. Nov	

Lipases hydrolyze triglycerides present in human sebum, producing the release of free unsaturated fatty acids, such as oleic acid and arachidonic acid, which are capable of crossing the epidermal barrier. These metabolites play a crucial role in the initiation of the inflammatory response, causing hyperproliferation and aberrant differentiation of keratinocytes, resulting in abnormalities in the corneum stratum such as parakeratosis, intracellular lipid droplets and abnormal development of stratum corneum cells[32]. Susceptibility to toxic metabolites, and therefore the development or not of SD, depends on innate differences in individuals. In turn, this innate susceptibility is given depending on the barrier of the corneum stratum, the permeability of the skin, as well as the immune response of the individual. Variations in these characteristics make an individual more susceptible or not to the epithelial barrier disruption induced by unsaturated fatty acids (Figure 1)[4,6,9].

At the cellular level, inflammatory activity is evidenced by the infiltration of leukocytes in the affected skin, including lymphocytes, NK cells, and neutrophils[11]. Finally, the AhR receptor ligands (malassezina, indirubin, indol [3,2-b] carbazole, formyl-indo [3,2-b] carbazole) produce a down-regulation of the respiratory burst of human neutrophils, as well as a decreased ability of dendritic cells to mature and present antigens upon stimulation of the TLR receptor (toll-like receptor)[25].

Secondly, an increase in the local immune response is evidenced through the production of different pro-inflammatory cytokines by the keratinocytes, such as IL-1α, IL-6, IL-8, and TNF-α, thus prolonging the inflammatory response triggered by these yeasts. Furthermore, arachidonic acid is a source of prostaglandins, which are pro-inflammatory mediators that can cause inflammation through neutrophil recruitment and vasodilation[9,11].

Thirdly, a sensitization to cross-reactive allergens produced by *Malassezia* can be evidenced. According to this model, there is an increased inflammatory response against the exposure to *Malassezia spp*. by the action of allergens released by the microorganism (e.g., Mala s1, 7-9, cyclophilin, thioredoxin). *M. sympodialis* secretes nano-vesicles containing allergens capable of inducing the release of inflammatory cytokines, mainly IL-4, which generate type IV hypersensitivity reactions, especially under conditions of a pH more alkaline than usual, both in healthy individuals as in individuals with atopic dermatitis and SD[26].

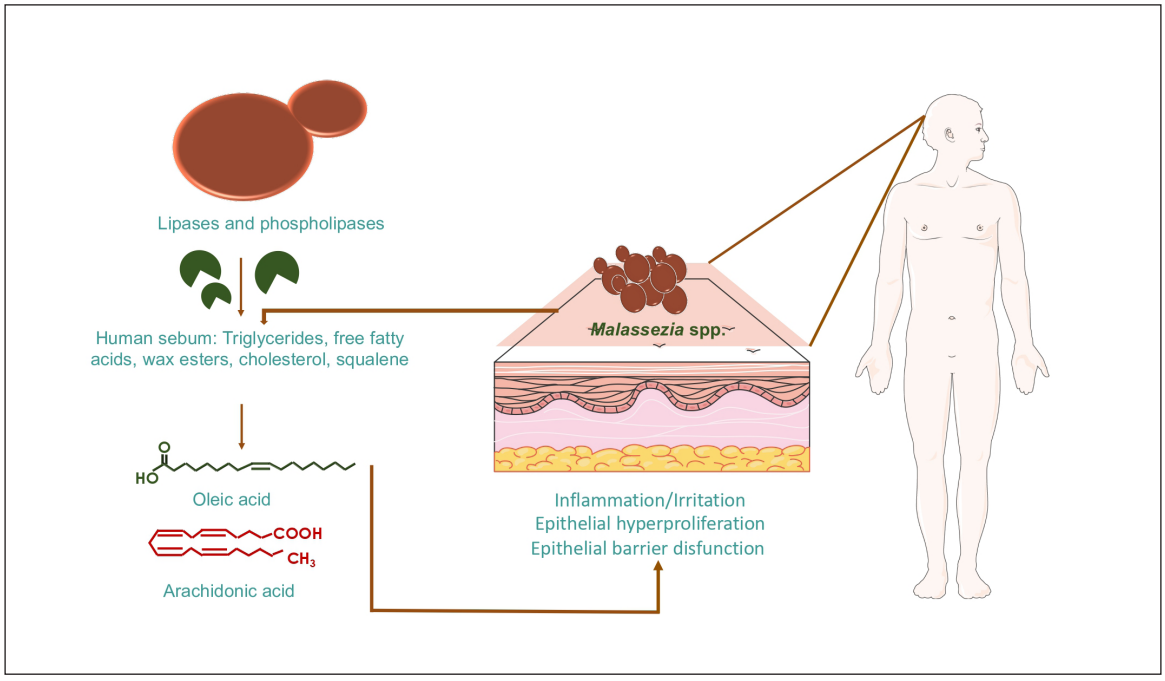

Figure 1. Role of *Malassezia* spp. lipid metabolism and their relation with the physiology of seborrhoeic dermatitis (DS). This figure was created using images from Servier Medical Art Commons Attribution 3.0 Unported License (http://smart.servier.com).

Malassezia and the host response

In the process of the interaction between two organisms, there are determinants specific of the immune response type established to the antigenic exposure. In the case of *Malassezia spp*., the maturation of dendritic cells derived from the monocytic line is the main cellular component that is responsible for the antigenic presentation and induction of a predominantly Th_2-type lymphocytic response**.** An alternative mechanism described, which contributes with the increase in the immune response against this microorganism, is the interaction of dendritic cells with NK and NKT cells in the skin for the removal of phagocytic cells with incorporated fungal antigens[27]**.** Recognition by PRR (Pattern Recognition Receptors) has also been reported, with the β-glucans being the PAMP (Pathogen-Associated Molecular Patterns) identified for *Malassezia spp*, which are recognized by the human type 1-dectins[28]**.** Some studies have also proposed chitin as a probable PAMP in the initial recognition of *Malassezia spp*[29]**.**

Regarding the characteristic itching in SD, the recognition of zymosan by the TLR-2 receptors has been established as the probable mechanism, with activation of second messengers (MyD88) and cross-reactivity with the high-affinity receptor for IgE (FceRI) on mast cells, triggering the release of histamine, proteases, chemotactic factors, IL-6 and arachidonic acid metabolites, all responsible for the characteristic itching[30].

In this scenario, the diversity of the interaction mechanisms still to be characterized represent an arsenal of opportunities as therapeutic targets for the prevention and treatment of dermatological pathologies associated with *Malassezia spp*.

Treatment

Therapy focuses on the control of acute episodes, as well as long-term maintenance without symptoms. The goals of the treatment are to eliminate lesions, prevent skin infections, as well as reduce the inflammation and associated itching. Treatment includes eliminating the cause of the disease (antifungal treatment or suppression of sebum secretion) and controlling cell proliferation and inflammation[4]. The first-line treatment has traditionally been the combination of an antifungal agent, usually topical, and a corticosteroid[31].

Topical use compounds

Among the compounds of topical used in the treatment of SD, we find antifungals (azoles, Ciclopirox, Octopirox, Bifonazol, Allylamines [Terbinafine]), coal tar, corticosteroids, Metronidazole, zinc pyrithione, selenium sulfide and immunomodulators (Pimecrolimus and Tacrolimus) (Table 2).

Antifungals

Ketoconazole is an antifungal compound of the imidazole group. It produces a disruption of the synthesis of ergosterol in fungi through its inhibitory action on one of the microsomal cytochrome P-450 enzymes, 14-α-sterol demethylase, and the inhibition of the synthesis of 5-lipoxygenase, which blocks the synthesis of the B_4 leukotriene, thereby conferring its anti-inflammatory properties[32]. For the treatment of SD, ketoconazole comes in four presentations: cream 2%, gel 2%, foam 2%, and shampoo 1-2%[33]. Shampoo with 2% ketoconazole is the most widely used form for the initial management of SD.

Table 2. Topical treatments for the treatment of seborrheic dermatitis

Drug (Reference)	Presentation	Application frequency	Adverse effects / Other information
Antifungals			
Ketoconazole[33-36]	2% Cream	Twice daily	Category C in pregnancy Irritation and burning sensation (<3% of patients)
	2% Gel	Once-daily	
	Foam	Twice daily	
	Shampoo	Once- twice per week	
Ciclopirox[34, 35, 37-40]	0,77% Gel	Twice daily	Category B in pregnancy Irritation and burning sensation
	1% Shampoo	Twice daily	
Terbinafine[23, 35, 41, 42]	1% Cream	Once-daily	Liver dysfunction Category B in pregnancy
Zinc pyrithione[43-46]	1% Shampoo	Once-daily for one week, then three times per day	Skin irritation No data in gestation
Corticosteroids			
Hydrocortisone[47-49]	1%-2,5% Cream	Twice daily	Category C in pregnancy
Immunomodulators			
Tacrolimus[56-57]	0,1% Ointment	Twice daily	Category C in pregnancy
Pimecrolimus[41, 51-55]	1% Cream	Twice daily	Lymphoma and skin cancer

Made by the authors
Category B = Animal studies have shown risks; human studies are negative or not adequate.
Category C = Animal studies are positive for fetal risk without human studies. The risk cannot be ruled out.

Seven double-blind, randomized controlled clinical trials using ketoconazole cream and shampoo with populations of up to 1162 individuals, showed a clinical recovery of up to 88% of the treated individuals[31]. A double-blind clinical trial included 1162 individuals, presenting mild to severe SD compromising multiple body regions. In this study, the treatment produced the complete resolution of symptoms and lesions, within the fourth week of treatment, in 56% of patients receiving ketoconazole 2% ointment twice daily, compared to 42% receiving placebo ($p<0.001$)[34]. A clinical trial, of 459 individuals with a moderate to severe SD and multiregional compromise, compared the ketoconazole 2% gel used once daily versus placebo. This study showed complete remission of lesions in 25% of patients receiving ketoconazole, compared to 14% in the placebo group on day 28 of treatment ($p=0.001$)[35].

Ciclopirox 1%, or cycloxisporamine, is a synthetic antifungal derived from hydroxypyridone and has been shown to have antifungal, antibacterial, and anti-inflammatory properties[33]. This medication works by inhibiting the absorption of essential components and altering cell permeability, disrupting the DNA, RNA, and protein synthesis[32]. In addition, ciclopirox chelates metal ions, restricting the availability of iron to the fungal cell and, in consequence, inhibiting the iron-dependent enzymes responsible for the degradation of peroxides within the fungal cell. The antifungal properties of ciclopirox, together with its tolerability and low rate of toxic effects, make it an ideal alternative for both the treatment and prophylaxis of SD[36]. A multicenter, randomized, double-blind clinical trial with 1000 patients with scaly erythematous lesions on the scalp found a total remission of the lesions within four weeks of administration in 45% of patients with one weekly application and 58% of patients with two weekly applications, compared to the placebo group with a 32% reduction ($p<0.001$)[37]. Other studies have shown ciclopirox effectiveness against a placebo, specifically in the concentration of 1%[38]. In the same group, the octopirox (Piroctone olamine), an hydroxamic acid, it's a topical agent that inhibits ergosterol synthesis. In the presentation of shampoo at 0.5-1%, has demostrared reduction in the erythema and pruritus with excellent results [39].

Terbinafine interferes with the fungal biosynthesis of sterols by inhibiting the squalene epoxidase enzyme, which leads to the intracellular accumulation of squalene. In addition to its antifungal properties, terbinafine for the topical application also has anti-inflammatory activity[40]. One study compared the efficiency of terbinafine 1% cream against the efficacy of ketoconazole 2% cream and placebo. A randomized, double-blind study included 90 patients with facial SD, performed a score of perceived symptoms, it found that the mean of total decrease of symptoms (erythema, itching, and exfoliation) went from 5.04 to 1.78 in the group receiving terbinafine, from 5.04 to 1.81 in the group receiving ketoconazole, and from 4.97 to 3.73 in the placebo group ($p=0.003$). However, when comparing terbinafine with ketoconazole, there is no significant difference ($p>0.05$)[41]. Another study suggested that terbinafine may be a useful alternative in infections with a low response to azoles[22].

Zinc pyrithione is an ionophore, which facilitates the transport of zinc through the membranes. This drug inhibits fungal growth through the increase of the cellular levels of copper, an ion responsible for altering sulfurous iron proteins, essential for fungal growth[42]. A randomized, double-blind study with 53 patients, presenting mild to moderate scalp SD, demonstrated the effectiveness of the active ingredient when compared to placebo ($p<0.05$). Furthermore, it was evidenced that the high deposit zinc pyrithione shampoo was significantly superior when compared to the very low deposit shampoo, in terms of both improving the severity of scaling and reducing the levels of *M. furfur*[43]. As to the effectiveness of zinc pyrithione compared to ketoconazole, several trials have shown a decreased effectiveness[44]. However, a satisfactory effect is obtained when used in combination with ketoconazole[45].

Corticosteroids

Topical corticosteroids are used for short periods and on a limited body area, to control the erythema and itching of acute episodes. These medications have anti-inflammatory properties and are active in rapidly eliminating visible signs and

associated symptoms. Their long-term use should be avoided due to their well-known side effects such as skin atrophy, telangiectasias, hypertrichosis, and perioral dermatitis[46].

Different randomized clinical trials have compared several topical corticosteroids used for short term periods, including hydrocortisone, betamethasone dipropionate, clobetasol 17-butyrate and clobetasol dipropionate with topical antifungals [47]. A recent study comparing the effectiveness of sertaconazole 2% cream with hydrocortisone 1% cream reported a 90% satisfaction in patients receiving sertaconazole and 83.3% in the group with hydrocortisone, the difference was not statistically significant[48]. A randomized, controlled clinical trial found that regimens containing clobetasol propionate were significantly more effective in ultimately reducing the severity of the disease than those receiving only ketoconazole ($p<0.05$)[49]. Despite this, so far, the evidence is limited to establish whether the combination of topical corticosteroids and topical antifungal agents confers a more significant benefit than a single-agent therapy[1].

Additionally, a significant association has been described in the increase of the values of the minimum inhibitory concentration for fluconazole and terbinafine secondary to the previous use of topical corticosteroids[22].

Immunomodulators- Calcineurin inhibitors

Pimecrolimus 1% cream and tacrolimus 0.03 and 0.1% ointment are part of the topical calcineurin inhibitors, which suppress the inflammatory activity associated with SD and prevent the side effects of steroids[50]. In addition to its traditional mechanism of action, both tacrolimus and pimecrolimus have been shown to have fungicidal activity[40]. Calcineurin inhibitors selectively inhibit the transcription and release of pro-inflammatory cytokines by T cells, by binding to a cytosolic receptor, the macrophillin-12 immunophilin[51]. The pimecrolimus-macrophillin complex inhibits the calcineurin protein, which results in the blocking of signal transduction pathways in T cells and the inhibition of the synthesis of inflammatory cytokines, specifically the Th_1 and Th_2 type cytokines, such as IL-2, IL-4, IFN-g, and TNF-α[52].

A randomized, double-blind study demonstrated that topical therapy with pimecrolimus 1% cream was effective and well-tolerated in the treatment of facial SD. Another randomized, double-blind clinical trial showed that 83% of the patients achieved complete elimination of symptoms after two weeks of application of pimecrolimus 1% cream[53]. Pimecrolimus has also been used for the treatment of SD in patients infected with HIV [54].

In respect to tacrolimus, a clinical trial reported its effectiveness as the betamethasone 17-valerate lotion or the zinc pyrithione shampoo[55]. Otherwise, a randomized clinical trial found a higher level of satisfaction in patients who received sertaconazole (90%) compared to the group receiving tacrolimus (83.3%); non-statistically significant results[56].

Metronidazole

This drug has antibacterial and antiparasitic activity. At the same time, it has a direct anti-inflammatory effect, which could be the key to its efficacy in different dermatological diseases[57]. A clinical trial found that metronidazole 1% gel was significantly more effective than placebo, with improvement after two weeks of starting treatment[58]. Other studies demonstrated the superiority of metronidazole when compared to placebo[59,60].

Fifty-one studies and 9052 participants were included in a systematic review conducted by Cochrane in 2015. It assessed the effect of different topical agents (ketoconazole, steroids, pimecrolimus, zinc pyrithione, ciclopirox, climbazole, metronidazole, lithium and herbal medicines) in comparison with placebo for the treatment of SD of the scalp and face in adolescents and adults [61]. The failure rate in itch resolution was found to be much lower in patients treated with ketoconazole 2% than with placebo (31% less risk of failure). Additionally, the resolution of erythema and scaling was better in ketoconazole treated versus placebo treated patients. On the other hand, ketoconazole and steroids were found to have similar effects in improving itching, erythema, and scaling, as well as in the rates of remission. However, the occurrence of side effects was 44% lower in the ketoconazole group of patients than in the steroids group. The study suggests that ketoconazole and ciclopirox are more effective than placebo and that, despite limited evidence, these two antifungals are more effective than any other agent in the same class.

Other topical therapies that should be considered are salicylic acid, selenium sulfide, sulfacetamide, glycerin, benzoyl peroxide, aloe vera and phototherapy. [62] Another topical alternative is the coal tar, compound that has been used traditionally worldwide for the treatment of Dandruff. Nevertheless, there is a concern about it's potential carcinogenicity, reason why it's use has decreased. Also some studies have demostrared that non tar shampoos (piroctone olamine, salicylic acid and elubiol), produce significantly better reduction of symptoms compared with de coal tar shampoos [63].

Oral use compounds

Oral antifungal therapy is indicated when multiple anatomic sites are involved, for patients who do not respond to traditional topical treatments, and patients with a severe development of SD[64].

Itraconazole is a member of the group of imidazoles, which shares the mechanism of action discussed for ketoconazole. Its use has significantly increased in the last decade, been the most studied antifungal in oral therapy. One of the main recommendations for its use is the inadequate response to topical corticosteroid treatments. In a systematic revision 6 clinical trials were found[64]. The treatment regimen, length, severity of the infection as well as the clinical and microbiological remission of each of the studies are represented in Table 3.

Table 3. Evidence of oral Itraconazole in the treatment of seborrheic dermatitis (DS)

Authors, year of publication (Type of study) (reference)	Regime	Treatment duration	DS severity	Clinical remission	Microbiological remission
Caputo *et al*., 2002 (CT)[65]	200mg / day for 7 days	One week	Not evaluated	93% a month after starting treatment	67% a month after starting treatment
Baysal *et al*., 2004 (CT)[66]	200 mg/day for seven days followed by 400 mg each month in two doses	12 months	No response to topical corticosteroid treatment	89.3% 12 months after starting treatment	79% 12 months after starting treatment
Kose *et al*., 2005 (CT)[67]	200 mg/day for seven days followed by 400 mg each month in two doses	Three months	Severe without response to topical corticosteroid treatment	58.6% three months after starting treatment	86% three months after starting treatment
Shemer *et al*., 2008 (CT)[68]	200 mg/day for 7 seven days followed by 200 mg every two weeks for 14 six	6 months	Moderate to severe	91.6% 24 weeks after starting treatment	40% 24 weeks after starting treatment
Das et *al*., 2011 (CT)[69]	200 mg/day for seven days followed by 400 mg each month in two weeks	3 months	Severe without response to topical corticosteroid treatment	83.3% 3 months after starting treatment	Not reported
Khondker et al., 2011(CT)[70]	200mg / day for seven days in the first month, followed by 200mg / day for two days the following 11 months	12 months	Not specified	88.46% good response at 12 weeks of treatment	Not reported
Abbas, Gholdsi & Abedeni, 2016 (CT)[71]	200mg / day for seven days followed by 200mg two days the following three months	Three months	Moderate to severe	73.7% one month after starting treatment	Not reported
Van, T., et al., 2019 (longitudinal)[72]	200mg / day for 14 days, followed by 200mg weekly for four weeks	Six months	Not specified	6.7% at two weeks, 63.4% upon completion of treatment	Not reported

** CT: Clinical Trial
Made by the authors

A double-blind, randomized controlled trial was conducted in 2016 on the effects of the itraconazole therapy on the quality of life of patients with a moderate to severe seborrheic dermatitis, an aspect that had not been evaluated in previous clinical trials. The impact of oral therapy with itraconazole versus placebo was assessed at the same time. The *Dermatology Life Quality Index* was implemented for the evaluation of the quality of life before and after treatment. It was found that itraconazole was superior compared to placebo, both in disease resolution and in the quality of life (p=0.001), with a 93.8% clinical improvement after two weeks, 87.5% after one month and 93.1% after four months. At the same time, the relapse rates were significantly lower with itraconazole[71]. The last study, of longitudinal type and shorter treatment (6 weeks), was carried out in 2019 and showed an acceptable response[72].

As for ketoconazole, one randomized controlled clinical trial and six case series support its use in SD. Ford et al. conducted a clinical trial with a 200 mg/day regimen of ketoconazole versus placebo. They found a more significant reduction in the severity of symptoms and the number of yeasts per field on direct examination, despite the absence of clinical or microbiological remission[73]. Nevertheless, in 2013 the FDA issued warnings against it clinical use due to the risk of liver injury, reason why it was withdrawn in Europe and Canada.

On the other hand, fluconazole showed that the decrease in the severity rate had no significant difference with the placebo group[64]. Another study compared the response to the fluconazole 200 mg regimen with placebo once a week and found a clinical and microbiological remission in the four patients studied[74].

For terbinafine, two single-blind controlled randomized clinical trials and one open, noncomparative trial have been carried out (Table 4). The *in-vitro* activity of the terbinafine against *Malassezia* has been estimated in comparison to itraconazole and ketoconazole, showing that it has the least inhibitory effect on growth in contrast to the other two compounds[75].

In recent years, the use of low doses of isotretinoin, a widely used drug for the management of acne, has been suggested. Its application has not been approved for seborrheic dermatitis. This drug contributes to a decreased sebum secretion by reducing the size of the sebaceous glands, curbing cell proliferation, and stimulating the apoptosis of sebum cells[79]. Furthermore, anti-inflammatory properties have been demonstrated with the reduction of pro-inflammatory cytokines[20]. This can be considered as a therapeutic option in patients with a moderate to severe SD, with facial and scalp involvement, however, more studies are required.

Table 4. Clinical trials with oral terbinafine in the treatment of seborrheic dermatitis (DS)

Study (reference)	Regime	Treatment duration	SD severity	Clinical remission	Microbiological remission
Scaparro *et al*., 2001[76]	250mg / daily	Four weeks + 8 weeks of follow-up	Moderate to severe	68% four weeks after starting treatment	12% four weeks after starting treatment
Vena *et al*., 2005 [77]	250mg / daily	Six weeks + 4 weeks follow-up	Moderate to severe	70% of the terbinafine group vs. 45.4% of the placebo group	Not reported
Cassano *et al*., 2002 [78]	250mg / daily for 12 days each month	Three months + 1-month follow-up	Moderate to severe with no response to topical corticosteroid treatment	22.2% three months after starting treatment	32% three months after starting treatment

Adapted from: Gupta, A. K., Richardson, M., & Paquet, M. (2014). A systematic review of oral medications for seborrheic dermatitis. *Journal of the European Academy of Dermatology and Venereology*, *28*(1), 16–26. https://doi.org/10.1111/jdv.12197

Finally, cases of systemic SD recalcitrant to the above-outlined management have been described in patients with comorbidities such as HIV and Parkinson's disease. Apremilast, a 4-phosphodiesterase inhibitor used to treat psoriasis, has been effectively used in 3 case reports of recalcitrant SD[80].

Conclusions

Seborrheic dermatitis is a clinical condition that affects a significant group of people, causing a high emotional and economic impact on individuals with this disease. Its etiology is not completely understood and it is considered to have a multifactorial origin. However, the dysbiosis processes seem to have a significant effect on the clinical presentation of the disease. The treatment of these conditions is equally diverse, with the use of antifungals for long periods, both topical and systemic, aspect that can also induce resistance in *Malassezia* as has been revealed recently. For this reason, it is essential to search for new therapeutic alternatives that favor the homeostasis of microorganisms in regarding host conditions. Besides, it is crucial to understand what is the role of this yeast in the interaction with other microorganisms, the host, and the SD.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of data. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. The authors declare that no data that enables identification of the patients appears in this article.

Funding. Autofinanced

Conflict of interest. The authors declare that the revision was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgment. The authors thank Dr. Elizabeth Castañeda for the critical review of this manuscript.

References

1. Naldi L, Diphoorn J. Seborrhoeic dermatitis of the scalp. *BMJ Clin Evid*. 2015;2015(November 2013):1-30.
2. Ashbee HR, Evans E. Glyn. Immunology of diseases associated with *Malassezia* species. *Clin Microbiol Rev*. 2002;15(1):21-57. doi:10.1128/CMR.15.1.21–57.2002
3. del Rosso JQ. Adult seborrheic dermatitis: A status report on practical topical management. *J Clin Aesthet Dermatol*. 2011;4(5):32-38.
4. Schwartz, J., DeAngelis, Y. and Dawson TJ. Dandruff and seborrheic dermatitis: a head scratcher. In: Evans T, Randall W, eds. *Practical Modern Hair Science*. Chicago: Alluredbooks; 2012:389–413.
5. Naldi L, Rebora A. Seborrheic Dermatitis. *N Engl J Med*. 2009;360(4):387-396. doi:10.1056/NEJMcp0806464
6. DeAngelis YM, Gemmer CM, Kaczvinsky JR, Kenneally DC, Schwartz JR, Dawson TL. Three etiologic facets of dandruff and seborrheic dermatitis: *Malassezia* fungi, sebaceous lipids, and individual sensitivity. *J Investig Dermatol Symp Proc*. 2005;10(3):295-297. doi:10.1111/j.1087-0024.2005.10119.x
7. Pedrosa AF, Lisboa C, Rodrigues A. *Malassezia* infections: A medical conundrum. *J Am Acad Dermatol*. 2014;71(1):170-176.
8. Hay RJ. *Malassezia*, dandruff and seborrhoeic dermatitis: An overview. *Br J Dermatol*. 2011;165(SUPPL. 2):2-8. doi:10.1111/j.1365-2133.2011.10570.x
9. Borda LJ, Wikramanayake TC. Seborrheic Dermatitis and Dandruff: A Comprehensive Review. *J Clin Investig Dermatology*. 2015;3(2):1-10. doi:10.13188/2373-1044.1000019
10. de Avelar J, Larangeira H, Pereira R, Martins P, Luiz H. Scalp seborrheic dermatitis: prevalence and associated factors in male adolescents. *Int J Dermatol*. 2012;51(1):46-49.
11. Schwartz J, Messenger A, Tosti A, et al. A Comprehensive Pathophysiology of Dandruff and Seborrheic Dermatitis – Towards a More Precise Definition of Scalp Health. *Acta Derm Venereol*. 2013;93(2):131-137. doi:10.2340/00015555-1382
12. Dréno B, Pécastaings S, Corvec S, Veraldi S, Khammari A, Roques C. *Cutibacterium acnes (Propionibacterium acnes)* and acne vulgaris: a brief look at the latest updates. *J Eur Acad Dermatology Venereol*. 2018;32:5-14. doi:10.1111/jdv.15043
13. Saxena R, Mittal P, Clavaud C, et al. Comparison of Healthy and Dandruff Scalp Microbiome Reveals the Role of Commensals in Scalp Health. *Front Cell Infect Microbiol*. 2018;8:346. doi:10.3389/fcimb.2018.00346
14. Chatzikokkinou P, Sotiropoulos K, Katoulis A, Luzzati R, G T. Seborrheic dermatitis - an early and common skin manifestation in HIV patients. *Acta Dermatovenerol Croat*. 2008;16(4):226-230.
15. Rincón S, Celis A, Sopó L, Motta A, Caridad M, De García C. *Malassezia* Yeast Species Isolated from Patients with Dermatologic Lesions. Vol 25.; 2005.
16. Amado Y, Patiño-Uzcátegui A, Cepero De García MC, et al. Seborrheic dermatitis: Predisposing factors and ITS2 secondary structure for *Malassezia* phylogenic analysis. *Med Mycol*. 2013;51(8):868-875. doi:10.3109/13693786.2013.820001
17. Theelen B, Cafarchia C, Gaitanis G, Bassukas ID, Boekhout T, Dawson TL. Correction: *Malassezia* ecology, pathophysiology, and treatment (Medical Mycology (2018) (S10-S25) DOI: 10.1093/mmy/myx134). *Med Mycol*. 2019;57(3):E2. doi:10.1093/mmy/myy046
18. Celis AM, Wösten H, Triana S, Restrepo S, de Cock H. *Malassezia* spp. beyond The Mycobiota. *SM Dermatolog J*. 2017;3(3):1-10. doi:10.36876/smdj.1019

19. Harada K, Saito M, Sugita T, Tsuboi R. *Malassezia* species and their associated skin diseases. *J Dermatol*. 2015;42(3):250-257. doi:10.1111/1346-8138.12700
20. Kamamoto CSL, Nishikaku AS, Gompertz OF, Melo AS, Bagatin E, Hassun KM. Cutaneous fungal microbiome: *Malassezia* yeasts in seborrheic dermatitis scalp in a randomized, comparative and therapeutic trial. *Dermatoendocrinol*. 2018;9(1):e1361573. doi:10.1080/19381980.2017.1361573
21. Lorch JM, Palmer JM, Vanderwolf KJ, et al. *Malassezia vespertilionis* sp. Nov.: A new cold-tolerant species of yeast isolated from bats. *Persoonia Mol Phylogeny Evol Fungi*. 2018;41:56-70. doi:10.3767/persoonia.2018.41.04
22. Pedrosa AF, Lisboa C, Faria-Ramos I, et al. Epidemiology and susceptibility profile to classic antifungals and over-the-counter products of *Malassezia* clinical isolates from a Portuguese University Hospital: a prospective study. *J Med Microbiol*. 2019;68(5):778-784. doi:10.1099/jmm.0.000966
23. Prohic A, Jovovic Sadikovic T, Krupalija-Fazlic M, Kuskunovic-Vlahovljak S. *Malassezia* species in healthy skin and in dermatological conditions. *Int J Dermatol*. 2016;55(5):494-504. doi:10.1111/ijd.13116
24. Velegraki A, Cafarchia C, Gaitanis G, Iatta R, Boekhout T. *Malassezia* infections in Humans and Animals: Pathophysiology, Detection, and Treatment. *PLoS Pathog*. 2015;11(1):e1004523. doi:10.1371/journal.ppat.1004523
25. Gaitanis G, Velegraki A, Mayser P, Bassukas ID. Skin diseases associated with *Malassezia* yeasts: Facts and controversies. *Clin Dermatol*. 2013;31(4):455-463. doi:10.1016/j.clindermatol.2013.01.012
26. Rayner S, Bruhn S, Vallhov H, Andersson A, Billmyre RB, Scheynius A. Identification of small RNAs in extracellular vesicles from the commensal yeast *Malassezia sympodialis*. *Sci Rep*. 2017;7. doi:10.1038/srep39742
27. Buentke E, D'Amato M, Scheynius A. *Malassezia* enhances natural killer cell-induced dendritic cell maturation. *Scand J Immunol*. 2004;59(5):511-516. doi:10.1111/j.0300-9475.2004.01416.x
28. Romani L. Immunity to fungal infections. *Nat Rev Immunol*. 2011;11(4):275-288. doi:nri2939 [pii]\r10.1038/nri2939
29. Vega K, Kalkum M. Chitin, chitinase responses, and invasive fungal infections. *Int J Microbiol*. 2012;2012:1-10. doi:10.1155/2012/920459
30. Selander C, Engblom C, Nilsson G, Scheynius A, Andersson CL. TLR2/MyD88-dependent and -independent activation of mast cell IgE responses by the skin commensal yeast *Malassezia sympodialis*. *J Immunol*. 2009;182(7):4208-4216. doi:10.4049/jimmunol.0800885
31. Picardo M, Cameli N. Seborrheic Dermatitis. In: *Evidence-Based Dermatology*. Oxford, UK: John Wiley & Sons, Ltd; 2014:169-174. doi:10.1002/9781118357606.ch25
32. Farhat E, Stein L. *Acneiform Eruptions in Dermatology*. (Zeichner J, ed.). New York, NY: Springer New York; 2014. doi:10.1007/978-1-4614-8344-1
33. Gupta AK, Batra R, Bluhm R, Boekhout T, Dawson TL. Skin diseases associated with *Malassezia* species. *J Am Acad Dermatol*. 2004;51(5):785-798. doi:10.1016/j.jaad.2003.12.034
34. Elewski B, Abramovits W, Kempers S, Schlessinger J. A novel foam formulation of ketoconazole 2% for the treatment of seborrheic dermatitis on multiple body regions. *J Drugs Dermatol*. 2007;6(10):1001-1008.
35. Elewski B, Ling M, Phillips T. Efficacy and safety of a new once-daily topical ketoconazole 2% gel in the treatment of seborrheic dermatitis: a phase III trial. *J Drugs Dermatol*. 2006;5(7):646-650.
36. Subissi A, Monti D, Togni G, et al. Ciclopirox: recent nonclinical and clinical data relevant to its use as a topical antimycotic agent. *Cochrane Database Syst Rev*. 2010;48(4):503-535. doi:10.1002/14651858.CD004685.pub2
37. Shuster S, Meynadier J, Kerl H, Nolting S. Treatment and prophylaxis of seborrheic dermatitis of the scalp with antipityrosporal 1% ciclopirox shampoo. *Arch Dermatol*. 2005;141(1):47-52. doi:10.1001/archderm.141.1.47
38. Abeck D, Henz B, Corte M, et al. Rationale of frequency of use of ciclopirox 1% shampoo in the treatment of seborrheic dermatitis: Results of a double-blind, placebo-controlled study comparing the efficacy of once, twice, and three times weekly usage. *Int J Dermatol*. 2004;43(SUPPL. 1):13-16. doi:10.1111/j.1461-1244.2004.02382.x
39. Piquero-Casals J, Hexsel D, Mir-Bonafé JF, Rozas-Muñoz E. Topical Non-Pharmacological Treatment for Facial Seborrheic Dermatitis. *Dermatol Ther (Heidelb)*. 2019;9(3):469-477. doi:10.1007/s13555-019-00319-0
40. Gupta AK, Nicol K, Batra R. Role of antifungal agents in the treatment of seborrheic dermatitis. *Am J Clin Dermatol*. 2004;5(6):417-422.
41. Azimi H, Golforoushan F, Jaberian M, Talghini S, Goldust M. Efficiency of terbinafine 1% cream in comparison with ketoconazole 2% cream and placebo in patients with facial seborrheic dermatitis. *J Dermatolog Treat*. 2013;(January):1-3. doi:10.3109/09546634.2013.806765
42. Reeder NL, Xu J, Youngquist RS, Schwartz JR, Rust RC, Saunders CW. The antifungal mechanism of action of zinc pyrithione. *Br J Dermatol*. 2011;165(SUPPL. 2):9-12. doi:10.1111/j.1365-2133.2011.10571.x
43. Bailey P, Arrowsmith C, Darling K, et al. A double-blind randomized vehicle-controlled clinical trial investigating the effect of ZnPTO dose on the scalp vs. antidandruff efficacy and antimycotic activity. *Int J Cosmet Sci*. 2003;25(4):183-188. doi:10.1046/j.1467-2494.2003.00183.x
44. Bonifaz A, er Araiza J, ia Baños-Segura C, Ponce-Olivera RM. Comparative Study of Two Treatment's Schemes for Seborrheic Dermatitis with Shampoo of Ciclopiroxolamine/Zinc Pyrithione/Keluamide (CPO/PZ/K). *Dermatología Cosmética, Médica y Quirúrgica*. 2015;13(3):188-193.
45. Mokos ZB, Kralj M, Basta-Juzbašić A, Jukić IL. Seborrheic dermatitis: An update. *Acta Dermatovenerologica Croat*. 2012;20(2):98-104.
46. Curkova AK, Simaljakova M. Seborrheic Dermatitis. In: Katsambas AD, Lotti TM, Dessinioti C, D'Erme AM, eds. *European Handbook of Dermatological Treatments*. Berlin, Heidelberg: Springer Berlin Heidelberg; 2015:867-877. doi:10.1007/978-3-662-45139-7_87
47. Stratigos JD, Antoniou C, Katsambas A, et al. Ketoconazole 2% cream versus hydrocortisone 1% cream in the treatment of seborrheic dermatitis. *J Am Acad Dermatol*. 1988;19(5):850-853. doi:10.1016/S0190-9622(88)70244-3
48. Goldenberg G. Optimizing treatment approaches in seborrheic dermatitis. *J Clin Aesthet Dermatol*. 2013;6(2):44-49.
49. Ortonne JP, Nikkels AF, Reich K, et al. Efficacious and safe management of moderate to severe scalp seborrhoeic dermatitis using clobetasol propionate shampoo 0.05% combined with ketoconazole shampoo 2%: A randomized, controlled study. *Br J Dermatol*. 2011;165(1):171-176. doi:10.1111/j.1365-2133.2011.10269.x
50. Cook BA, Warshaw EM. Role of Topical Calcineurin Inhibitors in the Treatment of Seborrheic Dermatitis. *Am J Clin Dermatol*. 2009;10(2):103-118. doi:10.2165/00128071-200910020-00003
51. Gupta AK, Chow M. Pimecrolimus: A review. *J Eur Acad Dermatology Venereol*. 2003;17(5):493-503. doi:10.1046/j.1468-3083.2003.00692.x
52. Carroll CL, Fleischer, Jr AB. Tacrolimus ointment: the treatment of atopic dermatitis and other inflammatory cutaneous disease. *Expert Opin Pharmacother*. 2004;5(10):2127-2137. doi:10.1517/14656566.5.10.2127
53. Ozden MG, Tekin NS, Lter N, Ankarali H. Topical pimecrolimus 1 cream for resistant seborrheic dermatitis of the face: An open-label study. *Am J Clin Dermatol*. 2010;11(1):51-54. doi:10.2165/11311160-000000000-00000
54. Kim GK, del Rosso J. Topical pimecrolimus 1% cream in the treatment of seborrheic dermatitis. *J Clin Aesthet Dermatol*. 2013;6(2):29-35.
55. Shin H, Kwon OS, Won CH, et al. Clinical efficacies of topical agents for the treatment of seborrheic dermatitis of the scalp : A comparative study. *J Dermatol*. 2009;36:131-137. doi:10.1111/j.1346-8138.2009.00607.x
56. Goldust M, Rezaee E, Raghifar R, Hemayat S. Treatment of seborrheic dermatitis: the efficiency of sertaconazole 2% cream vs. tacrolimus 0.03% cream. *Ann Parasitol*. 2013;59(2):73-77.
57. Zip CM. Innovative Use of Topical Metronidazole. *Dermatol Clin*. 2010;28(3):525-534. doi:10.1016/j.det.2010.03.015
58. Parsad D, Pandhi R, Negi KS, Kumar B. Topical Metronidazole in Seborrheic Dermatitis – A Double-Blind Study. *Dermatology*. 2001;202(1):35-37. doi:10.1159/000051582
59. Ozcan H, Seyhan M, Yologlu S. Is metronidazole 0.75% gel effective in the treatment of seborrhoeic dermatitis? A double-blind, placebo controlled study. *Eur J Dermatol*. 2007;17(4):313-316. doi:10.1684/ejd.2007.0206
60. Siadat AH, Iraji F, Shahmoradi Z, Enshaieh S. The efficacy of 1 % metronidazole gel in facial seborrheic dermatitis : A double blind study. 2006;72(4):4-8.
61. Okokon EO, Verbeek JH, Ruotsalainen JH, Ojo OA, Bakhoya VN yange. Topical antifungals for seborrhoeic dermatitis (Review). *Cochrane database Syst Rev*. 2015;CD008138(5):1-224. doi:10.1002/14651858.CD008138.pub3
62. Borda LJ, Perper M, Keri JE. Treatment of seborrheic dermatitis: a comprehensive review. *J Dermatolog Treat*. 2018;0(0):1-12. doi:10.1080/09546634.2018.1473554
63. Piérard-Franchimont C, Piérard GE, Vroome V, Lin GC, Appa Y. Comparative anti-dandruff efficacy between a tar and a non-tar shampoo. *Dermatology*. 2000;200(2):181-184. doi:10.1159/000018362
64. Gupta AK, Richardson M, Paquet M. Systematic review of oral treatments for seborrheic dermatitis. *J Eur Acad Dermatology Venereol*. 2014;28(1):16-26. doi:10.1111/jdv.12197
65. Caputo R BM. Itraconazole: new horizons. *G Ital Dermatol Venereol*. 2002;137:1-7.
66. Baysal V, Yildirim M, Ozcanli C CA. Itraconazole in the treatment of seborrheic dermatitis: a new treatment modality. *Int J Dermatol*. 2004;43:63-66.
67. Kose O, Erbil H GA. Oral itraconazole for the treatment of seborrhoeic dermatitis: an open, noncomparative trial. *J Eur Acad Dermatol Venereol*. 2005;19:172-175.

68. Shemer A, Kaplan B NN et al. Treatment of moderate to severe facial seborrheic dermatitis with itraconazole: an open non-comparative study. *Isr Med Assoc J*. 2008;10:417-418.
69. Das J, Majumdar M CY et al. Oral itraconazole for the treatment of severe seborrhoeic dermatitis. *Indian J Dermatol*. 2011;56:515-516.
70. Khondker L, Choudhury AM, Wahab MA KM. Efficacy of oral itraconazole in the treatment of seborrheic dermatitis. *J Bangl Coll Phys Surg*. 2012;29:201-206.
71. Abbas Z, Ghodsi S, Abedeni R. Effect of itraconazole on the quality of life in patients with moderate to severe seborrheic dermatitis: a randomized, placebo-controlled trial. *Dermatol Pract Concept*. 2016;6(3). doi:10.5826/dpc.0603a04
72. Van TN, Hoang Thi N, Hoang Van T, et al. Efficacy of oral itraconazole in the treatment of seborrheic dermatitis in Vietnamese adults patients. *Open Access Maced J Med Sci*. 2019;7(2):224-226. doi:10.3889/oamjms.2019.056
73. Ford GP, Farr PM, Ive FA, Shusters S. The response of seborrhoeic dermatitis to ketoconazole. *Br J Dermatol*. 1984;111(5):603-607. doi:10.1111/j.1365-2133.1984.tb06631.x
74. Zisova L. Treatment of *Malassezia* species associated seborrheic blepharitis with fluconazole. *Folia Med* . 2009;51(3):57-59.
75. Sancak B, Ayhan M, Karaduman A, Arikan S. In vitro activity of ketoconazole, itraconazole and terbinafine against *Malassezia* strains isolated from neonates. *Mikrobiyol Bul*. 2005;39(3):301-308.
76. Scaparro E, Quadri G VG et al. Evaluation of the efficacy and tolerability of oral terbinafine (Daskil_) in patients with seborrhoeic dermatitis.A multicentre, randomized, investigator-blinded, placebo-controlled trial. *Br J Dermatol*. 2001;144:854-857.
77. Vena GA, Micali G SP et al. Oral terbinafine in the treatment of multi-site seborrhoic dermatitis: a multicenter, double-blind placebo-controlled study. *Int J Immunopathol Pharmacol*. 2005;18:745-753.
78. Cassano N, Amoruso A, Loconsole F VG. Oral terbinafine for the treatment of seborrheic dermatitis in adults. *Int J Dermatol*. 2002;41:821-822.
79. de Souza Leão Kamamoto C, Sanudo A, Hassun KM, Bagatin E. Low-dose oral isotretinoin for moderate to severe seborrhea and seborrheic dermatitis: a randomized comparative trial. *Int J Dermatol*. 2017;56(1):80-85. doi:10.1111/ijd.13408
80. Cohen SR, Gordon SC, Lam AH, Rosmarin D. Recalcitrant Seborrheic Dermatitis Successfully Treated With Apremilast. *J Cutan Med Surg*. 2020;24(1):90-91. doi:10.1177/1203475419878162