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REVIEW

Efficacy and Safety of Isotretinoin for Moderate-to-Severe Seborrheic Dermatitis: A Systematic Review of Randomized Controlled Trials

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Abstract: This study provide a comprehensive analysis of using oral isotretinoin as a promising therapy for severe to moderate seborrheic dermatitis, which is a chronic inflammatory skin condition that results in scaling as well as erythema that affects specific sites of the skin such as the scalp, face, upper trunk, or flexures. However, the exact cause of this condition is unclear.Various internal and external factors are associated with its pathogenesis. It is believed that the main factor is the overgrowth of Malassezia yeast, which is a part of the normal skin flora,proliferates in the sebum-rich areas.Other causes include host related factors like genetic predisposition, altered inflammatory responses as well as immune dysregulation, caused by conditions such as HIV or malignancies. In addition, neurophysiological and environmental factors can influence the disease onset. Cold climate, stress, and neurological disorders such as Parkinson's disease all are key factors influencing the onset and relapse of the disease.Pathogenesis involves a complicated interaction between microbial, immunological, and epidermal factors. Malassezia antigens and metabolites in predisposed individuals can trigger both innate and adaptive immunity leading to inflammatory reactions. In addition, Malassezia's lipase activity damages the skin barrier by.producing unsaturated fatty acids, leading to raised epidermal turnover and scaling.

Keywords: isotretinoin, seborrheic dermatitis, randomized controlled trial

Introduction

Seborrheic dermatitis is a recurrent, inflammatory, and chronic skin disease. Typically, it only affects specific skin areas like the scalp, face, upper trunk, or flexures.[1] Seborrheic dermatitis appears in humans at two stages of their lives: infancy and adulthood.[2] Although the exact cause of this disorder is unknown, multiple exogenous and endogenous factors have been implicated in its pathogenesis.[3] Different methods are used to treat seborrheic dermatitis, based on the severity of the case itself. If the condition is severe and does not respond well to topical treatments, systemic medications may be prescribed instead. Itraconazole is a well-known systemic anti-fungal with the highest percentage of cases with successful management outcomes, according to the currently available data.[4,5] In addition, oral isotretinoin, which is a synthetic retinoid used mostly to treat severe or moderately resistant acne, has gained considerable attention as a potential treatment for this condition because of its ability to decrease sebaceous gland activity as well as the amount of oil in acne, by reducing sebaceous gland size, decreasing proliferation, and inducing basal sebocyte apoptosis, it is

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believed to be a promising candidate for the treatment of this condition.[6] Orfanos and Zouboulis were the first to report low-dose oral Isotretinoin (0.10 mg/kg) for treating severe seborrhea.[7] In the studies by Geissler et al, an alternative regimen has been introduced for seborrhea associated with acne.[8] Because Isotretinoin is a powerful systemic medicine, the risk-benefit ratio must be carefully considered, especially when it comes to dealing with a condition that is non-life threatening, such as seborrheic dermatitis. Despite these facts, the data currently available on the use of Isotretinoin for moderate-to-severe seborrheic dermatitis has significant gaps regarding its safety and efficacy when compared to classical therapies. To ensure that these gaps are filled, a more thorough and in-depth review of the literature will be valuable. Therefore, additional studies must be conducted to clarify how isotretinoin can be utilized for this condition. Conducting further studies is crucial to justify and explain using Isotretinoin in this condition. In this analysis, the safety and effectiveness of isotretinoin will be compared to placebo and other established therapies. In conclusion, this research will provide more light on the role of isotretinoin and point out areas that need more research, which will help to direct clinical practice and guide future studies.

Methods & Materials

Review of the Literature

In our review, we adhered to the PRISMA (Preferred Reporting Items of Systematic Reviews and Meta-Analysis) model to ensure that studies were selected with a minimal amount of bias.[9] This study protocol was registered in advance with PROSPERO and assigned the ID: CRD42024575601.[10] Given the nature of the research, obtaining ethical approval was not required. In August 2024, we conducted a systemic search of the specified databases: (1) PubMed, (2) Google Scholar, and (3) Cochrane. A search was performed using the following keywords: (Isotretinoin OR isotretinion OR Accutane) and (seborrheic dermatitis OR seborrhoeic dermatitis OR seborrhea). Studies were regarded for the review depending on the PICOTS (population, intervention, comparison, outcome, time, setting) criteria.[11]

Methodology for Selecting Studies

For the inclusion criteria in our systematic review, the studies had to meet the following criteria: (1) they had to be in the English language, (2) the patients had to be diagnosed with moderate-to-severe seborrheic dermatitis, (3) the patients had to be treated with isotretinoin, (4) the studies had to compare patients with placebo or other standard treatments for seborrheic dermatitis, (5) measures of efficacy (eg, symptom improvement, quality of life) and safety (eg, adverse effects) had to be reported, and (6) the study had to be a randomized controlled trial. Studies were excluded from our systematic review based on the following criteria: (1) studies focusing on mild seborrheic dermatitis or other dermatological conditions without a specific focus on seborrheic dermatitis, (2) studies not involving isotretinoin as the primary intervention, (3) studies that had a lack of a comparative group (placebo or standard treatment), (4) studies that do not report relevant efficacy or safety outcomes, (5) studies that were of the following: non-randomized studies, case reports, animal studies, and retrospective studies, and (6) studies that were not of the English language.

Process of Screening and Data Extraction

Four independent reviewers simultaneously and independently screened the papers, evaluating them based on their titles and abstracts using the Rayyan web-based tool.[12] Subsequently, the full texts of the selected articles were reviewed concurrently by all reviewers, with any discrepancies being resolved. Following this process, data extraction was carried out by two reviewers, focusing on the following variables: (1) study design, (2) total number of participants, (3) gender distribution, (4) measures of efficacy, (5) measures of safety, and (6) other relevant outcomes.

Assessment of Quality and Bias Risk

We evaluated the quality and bias in each study included in our study by employing the suitable methodology specific to the study's design. In the case of randomized controlled trials (RCTs), we employed the Cochrane risk of bias for randomized trials (RoB2) technique to assess six specific areas: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other forms of bias.[13] Two reviewers conducted separate assessments of the potential for bias in

each study, and any discrepancies were resolved by seeking input from a third reviewer. The overall risk of bias for each study was determined to be low based on the evaluation of specific domains.

Results

The Literature's Findings

Our systematic search across PubMed/Medline and Google Scholar, Cochrane yielded a total of 289 publications related to the treatment of seborrheic dermatitis. After removing duplicates, 236 records were screened by title and abstract. A total of 16 full-text articles were assessed for eligibility, of which 14 were excluded based on our criteria. Ultimately, only 2 studies were included in the systematic review (Figure 1). These studies, published between 2016 and 2018, were conducted in Brazil and Iraqi Kurdistan, respectively. Both studies were randomized comparative trials, focusing on the efficacy and safety of low-dose oral isotretinoin compared to other treatments for seborrheic dermatitis.

A Description of the Characteristics of the Included Studies

The two studies included in this review were as follows:

Meran, 2018: Conducted in Erbil City, Iraqi Kurdistan, this randomized, parallel-group comparative study involved 68 patients. The study compared the efficacy of low-dose oral isotretinoin and oral itraconazole in treating seborrheic dermatitis. Isotretinoin was given at 20 mg twice weekly for three months, while itraconazole was administered 200 mg/day during the first week of month one, followed by 200 mg/day for two days at the start of months two and three

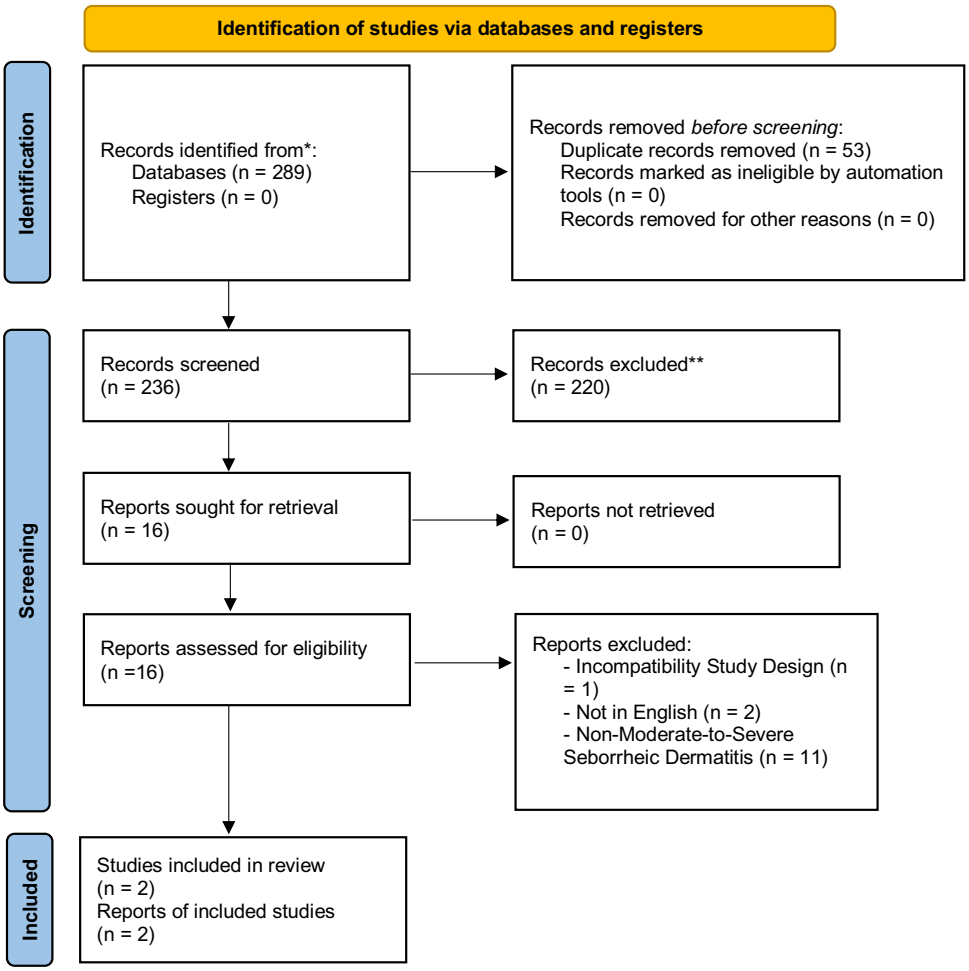

Figure 1 The flowchart of the reviewed studies according to PRISMA.
Note: *Records identified from databases and registers.** Records excluded during the screening phase.

Table 1. Participants' mean age was 31.26 years, with a standard deviation of 14.15 years. The follow-up duration was one month after a three-month treatment period. Primary outcomes consisted of the Seborrheic Dermatitis Area Severity Index (SDASI) score, and secondary outcomes included assessments of burning sensation and itching.[14]

Kamamoto, 2016: Conducted in Brazil, this randomized comparative clinical trial included 45 patients. The study compared low-dose oral isotretinoin with topical antiseborrheic treatment. Isotretinoin was given 10 mg every other day for six months, while the control group received topical therapy only Table 1. The mean age was 28.7 years with a standard deviation of 5.8 years for the isotretinoin group and 29.8 years with a standard deviation of 6.5 years for the comparison group. The follow-up period lasted six months. Primary outcomes included reductions in sebum production, patient opinion, investigator assessment, and quality of life scores. Secondary outcomes included clinical assessments of scalp pruritus, erythema, and scaling.[15]

Patient-Reported Outcomes, Complications, and Clinical Outcomes

Both studies reported improvements in the primary outcomes. The Meran study found that low-dose oral isotretinoin was more effective than oral itraconazole in reducing the severity of seborrheic dermatitis, as measured by the SDASI score. In the Kamamoto study, both treatments improved quality of life scores, though specifics on the comparative efficacy were less detailed. Patient-reported outcomes in both studies included subjective assessments of itching and burning sensations. Both studies did not detail severe complications, but they did note minor treatment-related complications like temporary dryness or irritation. Table 2 presents a comprehensive summary of patient-reported outcomes and complications.

Analyzing Biases, Assessing Quality, and Determining the Level of Evidence

The quality of the studies included was assessed using established tools for randomized controlled trials. Both studies adhered to rigorous methodology, but with some limitations in sample size and follow-up duration. The Meran study was rated as having moderate quality due to its smaller sample size and short follow-up period. The Kamamoto study, while providing a longer follow-up and a more comprehensive assessment of quality of life, also faced limitations related to its sample size and the lack of blinding Table 3.

Table 1 Summary of Included Studies and Treatment Regimens

Study	Group	Drug/ Intervention	Dose & Regimen	Duration	Adjunctive Therapy
Meran, 2018[14]	Isotretinoin (n=37)	Oral isotretinoin	20 mg twice weekly	3 months	1% hydrocortisone ointment (daily, 2 weeks) + 2% ketoconazole shampoo (3×/week, 2 weeks)
Meran, 2018[14]	Itraconazole (n=31)	Oral itraconazole	200 mg/day (week 1, month 1) → 200 mg/day for 2 days at start of months 2 and 3	3 months	Same as above
Kamamoto, 2016[15]	Isotretinoin	Oral isotretinoin	10 mg every other day	6 months	None
Kamamoto, 2016[15]	Control	Topical only	–	6 months	Antiseborrheic shampoo 3×/week + salicylic acid soap 2×/day

Table 2 Patient-Reported Outcomes and Complications

Study	Patient Satisfaction	Major Complications	Minor Complications	Follow-Up Duration
Meran, 2018[14]	High satisfaction reported	None reported	Transient dryness, irritation	1 month after treatment
Kamamoto, 2016[15]	Both treatments improved QoL	None reported	Minor dryness, irritation	6 months

Table 3 Bias Risk Assessment

Study ID	Authors/Year	Study Type	Risk of Bias Tool	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Overall RoB	Comments
S001	Meran, 2018[14]	RCT	Cochrane RoB	High	Low	Low	Low	Low	None	Low	Well-balanced groups, and each group follows the instructions
S002	Leao Kamamoto, 2016[15]	RCT	Cochrane RoB	High	Low	Low	Low	Low	None	Low	Well follow-up

Notes: A total of 2 studies were included in this systematic review, consisting of 2 RCTs studies. The risk of bias assessment for the included RCTs using the Cochrane Collaboration ROB tool revealed that 1 study had a low risk of bias, and 2 had a low risk of bias. The most common source of bias was selection bias.

Discussion

The point of this study was to find out if isotretinoin, a drug that is often used to treat acne, was safe and effective for treating mild to severe seborrheic dermatitis. The findings show that isotretinoin minimizes symptoms and enhances patients' quality of life. Current evidence suggests that isotretinoin is better than placebo or standard medication in many cases. The primary treatments for seborrheic dermatitis typically include topical antifungals and corticosteroids, particularly in milder cases. In more severe cases, the consideration of oral antifungals or isotretinoin may be required. Additionally, recent studies have explored other alternative treatments, such as Glycyrrhetinic Acid Complex, which has demonstrated efficacy in SD management.[16] For example, Wang HC et al conducted a randomized controlled trial showing significant improvement in seborrheic dermatitis symptoms with Glycyrrhetinic Acid Complex compared to placebo.[17] This suggests that Glycyrrhetinic Acid Complex may be considered as an alternative or adjunctive therapy, especially in cases unresponsive to conventional treatments.

Ongoing debate exists regarding the long-term efficacy of isotretinoin compared to conventional treatments. This study demonstrated that isotretinoin offers superior symptom management and enhances patient satisfaction compared to standard topical therapies, despite the occurrence of mild side effects such as dryness, which is generally well-tolerated by most patients. Orfanos and Zouboulis' prior study established the basis for using low-dose isotretinoin in the treatment of seborrhea.[18] Geissler et al provided evidence supporting the efficacy of very low-dose isotretinoin in controlling seborrhea, particularly in cases associated with acne. Their study demonstrated significant reductions in sebum production and improvement in clinical symptoms, highlighting isotretinoin as a valuable therapeutic option for patients with seborrhea secondary to acne[8.] Kamamoto et al conducted a randomized comparative trial evaluating low-dose oral isotretinoin (10–20 mg daily) in patients with moderate-to-severe seborrhea or seborrheic dermatitis, and reported significant reductions in erythema, scaling, and sebum production, supporting its role as an effective treatment for seborrhea beyond acne control.[15] This research study highlights the advantages of using isotretinoin for the treatment of seborrheic dermatitis. This study demonstrates the efficacy of isotretinoin in treating moderate-to-severe seborrheic dermatitis, especially in patients unresponsive to topical therapies. Isotretinoin has the potential to significantly improve the management of severe cases by decreasing sebum production and irritation. The standard treatment for seborrheic dermatitis typically includes topical antifungals and mild corticosteroids, which are effective for most patients. When these medications prove ineffective, isotretinoin provides an alternative with improved long-term outcomes for certain patients. Managing side effects such as dryness is crucial; however, isotretinoin may alter the approach to more complex cases of this condition. More studies are required to better understand isotretinoin's long-term safety and efficacy. Only extensive, worldwide, randomized studies can provide a more thorough safety and effectiveness profile. Isotretinoin's long-term safety and effectiveness may be better understood by following patients for many years, ideally five to ten. Future studies should explore the effectiveness of combination therapy to improve treatment results and more safely treat complicated cases of seborrheic dermatitis.

Limitations

- Small Sample Size: Since there are only two included studies, there is limited generalization; a larger sample of studies may give a wider understanding of the efficacy and safety of isotretinoin for seborrheic dermatitis.
- Geographic Limitations: Studies conducted in different regions, such as Brazil and Iraqi Kurdistan, have limited applicability for wider and diverse populations.
- Language bias: Only English-language studies were included, which may have excluded relevant research published in other languages.
- Only two RCTs were available, limiting the possibility of conducting a meta-analysis or robust statistical comparison.
- Inability to perform a pooled analysis due to heterogeneity in interventions and outcomes.

Conclusion

According to the study, low-dose oral isotretinoin is effective in treating moderate-to-severe seborrheic dermatitis, as it significantly improves clinical scores and symptoms with only moderate adverse events. Clinicians should consider isotretinoin as an option for patients who do not respond adequately to first-line therapies, such as topical antifungals or corticosteroids It may be necessary for more research to be conducted in the next 5–10 years regarding therapeutic measures and safety.

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Disclosure

The authors do not have any conflict of interest.

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