Research Article Volume 01, Issue No. 01. 2024

The International Medical Journal of Dermatology and Venereology

The Analysis Study of Rosacea Treatment with Low-Dose Isotretinoin: A Comprehensive Systematic Review

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Article History :
Received date : 2024/07/09
Revised date : 2024/08/03
Accepted date : 2024/09/02
Published date : 2024/10/07

ABSTRACT

Background: Rosacea is a chronic inflammatory skin condition that typically develops in the third decade of life but can occur at any age. Isotretinoin, traditionally used for acne, has been studied for rosacea due to its anti-inflammatory and sebum-reducing properties. However, concerns over adverse effects, including teratogenicity, have limited its use. **Methods:** Following PRISMA 2020 guidelines, this systematic review focused exclusively on full-text articles published in English between 2014 and 2024. **Result:** The study conducted a comprehensive review of over 100 publications sourced from reputable databases, including ScienceDirect, SagePub, and PubMed. Following an initial screening, eight publications were identified as warranting more in-depth analysis. Consequently, a thorough review of these selected studies was performed to ensure a detailed and rigorous evaluation. **Conclusion:** Low-dose isotretinoin is an effective treatment for moderate-to-severe or recalcitrant rosacea. All studies reviewed indicate that LDI improves symptoms with generally mild, dose-dependent side effects. LDI should be considered a valuable therapeutic option for rosacea, especially for patients who do not respond to traditional treatments.

Keyword: isotretinoin, low-dose, rosacea

INTRODUCTION

Rosacea is a chronic inflammatory skin condition that typically develops in the third decade of life but can occur at any age. It primarily affects the central face in a symmetrical pattern and can involve ocular and extra-facial areas. Symptoms include transient or persistent redness, papules, pustules, and nodules, which significantly impact quality of life. The condition is more common in women with lighter skin tones, affecting 1%–22% of adults, with a genetic predisposition in about 20% of cases.[1–3]

Rosacea presents in four main subtypes: erythematotelangiectatic (ETR), papulopustular (PPR), phymatous (PR), and ocular rosacea. Its pathogenesis remains unclear, but factors like Demodex folliculorum overgrowth, abnormal immune response, and environmental triggers such as UV light and spicy foods are thought to play a role. Current treatments include topical and oral anti-inflammatory or antimicrobial agents.[4,5]

Isotretinoin, traditionally used for acne, has been studied for rosacea due to its anti-inflammatory and sebum-reducing properties. However, concerns over adverse effects, including teratogenicity, have limited its use. Low-dose isotretinoin (LDI; ≤0.5 mg/kg/day) offers a safer alternative with fewer side effects.[6–8]

This systematic review investigated the efficacy and safety of LDI for the treatment of rosacea, focusing on its impact on lesion count, erythema, and relapse rates.

METHODS

Protocol

The investigation was carried out with scrupulous conformity to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 criteria, guaranteeing strict respect to accepted methodological principles. Strictly following PRISMA 2020 standards demonstrates a dedication to improving the clarity, replicability, and systematic thoroughness of the review process. The study incorporated thorough methodologies for conducting literature searches,

extracting data, and synthesizing findings. These methods were well implemented to minimize biases and guarantee the strength of the conclusions.

Criteria for Eligibility

The present study offers a comprehensive examination of the studies undertaken throughout the last ten years. Through the methodical examination and integration of data from other studies, this research seeks to clarify patterns and guide the improvement of patient care approaches for this group with multiple health conditions.

In order to guarantee the thoroughness and precision of the study, strict criteria for inclusion and exclusion were implemented. Only English-language peer-reviewed papers published from 2014 to 2024 were considered suitable for inclusion. Materials eligible for inclusion must also possess a DOI for the purpose of confirming their authenticity. In order to preserve the focus and integrity of the dataset, the analysis in question deliberately omitted non-research materials, including reviews, editorials, and duplicate entries from the same publication.

The systematic methodology employed in this study guarantees that the data used is both pertinent and trustworthy, therefore establishing a strong basis for deriving significant findings and progressing clinical practice.

Search Strategy

We used " ((isotretinoin) AND (low-dose)) AND (rosacea)" as keywords. The search for studies to be included in the systematic review was carried out using the PubMed, SagePub, and Sciencedirect databases.

Data retrieval

The authors conducted a thorough preliminary review of each article by examining its abstract and title to assess relevance before proceeding with a more detailed investigation. Only studies that aligned with the study's objectives and met the predefined inclusion criteria were considered for further review. This method allowed for the identification of a clear and consistent pattern across the research.

Full-text articles were restricted to those published in English to maintain consistency in the language of the studies. A rigorous screening process was applied to select content that was directly relevant to the study's focus and adhered to all established inclusion criteria. Articles not meeting these criteria were systematically excluded from further analysis and not included in the final evaluation.

The evaluation process included a comprehensive review of various factors such as study design, titles, authors, publication dates, research locations, and methodologies. This meticulous approach ensured that the content analyzed was of the highest relevance and quality, thereby strengthening the overall findings of the study.

Quality Assessment and Data Synthesis

The authors performed a meticulous review of each article's abstract and title to identify those deserving further investigation. After this initial screening, all relevant documents underwent a comprehensive examination. The results of this evaluation guided the selection of review papers, ensuring that only the most pertinent studies advanced to detailed analysis. This rigorous approach streamlined the selection process and facilitated a thorough and nuanced assessment of the existing research and its context.

Table 1. Search Strategy

Database	**Search Strategy**	***Hits***
Pubmed	((isotretinoin) AND (low-dose)) AND (rosacea)	7
Science Direct	((isotretinoin) AND (low-dose)) AND (rosacea)	79
Sagepub	((isotretinoin) AND (low-dose)) AND (rosacea)	17

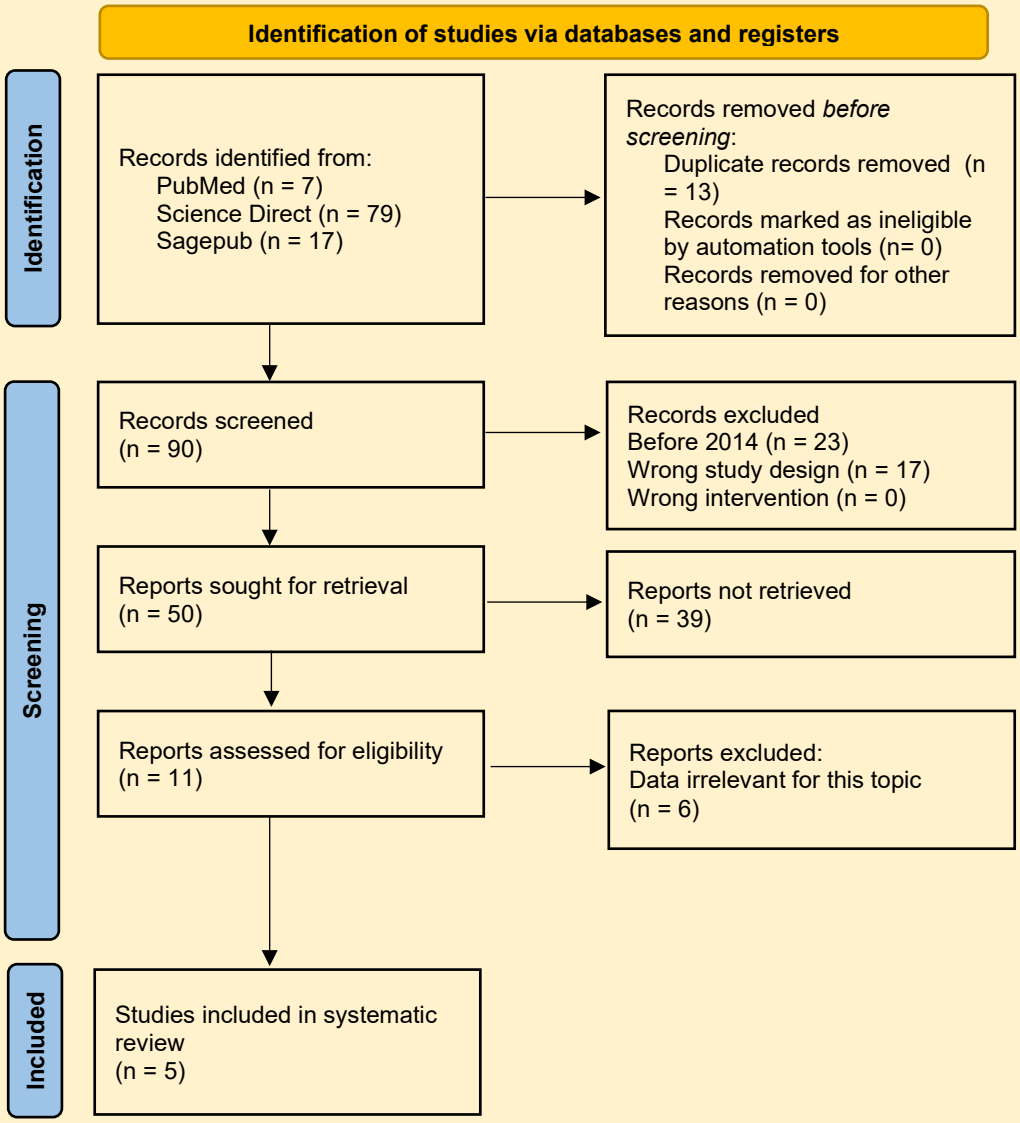

Figure 1. Article search flow chart

Table 2. Critical appraisal of Study

Parameters	Andrade (2020)	Sbidian (2016)	Shemer (2021)	Kwon (2020)	Rademaker (2018)
1. Bias related to temporal precedence Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes
2. Bias related to selection and allocation Was there a control group?	No	Yes	No	No	No
3. Bias related to confounding factors Were participants included in any comparisons similar?	No	No	No	No	No
4. Bias related to administration of intervention/exposure Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Yes.	Yes.	Yes.	Yes.	Yes.
5. Bias related to assessment, detection, and measurement of the outcome Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	No	No	No	No	No
Were the outcomes of participants included in any comparisons measured in the same way?	Yes	Yes	Yes	Yes	Yes
Were outcomes measured in a reliable way?	Yes	Yes	Yes	Yes	Yes
6. Bias related to participant retention Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	No	Yes	No	No	No
7. Statistical conclusion validity Was appropriate statistical	Yes	Yes	Yes	Yes	Yes

analysis used?

RESULT

We initiated the investigation by systematically gathering a significant assortment of papers from reputable sources such as Science Direct, PubMed, and SagePub. After a thorough three-stage screening process, we selected eight papers that were considered very pertinent to our ongoing systematic inquiry. Subsequently, we selected certain topics for further examination and meticulously evaluated each report. In order to expedite our study, we have included a concise summary of the evaluated information in Table 3.

Table 3. The literature included in this study

Author	Origin	Method	Sample	Result
Andrade, et al.[9] (2020)	Brazil	RCT	39 patients	The present study included 39 patients (30 females and 9 males). Best-corrected visual acuity was > 20/30 in >90% of patients in both groups and did not change after treatment. After treatment, improvement in ocular symptoms and meibomian gland dysfunction was more pronounced in group B ($p<0.05$); the other parameters did not reach statistical significance.
Sbidian, et al.[10] (2016)	France	RCT	156 patients	Between February 2007 and August 2009, 156 patients were randomized to receive either isotretinoin (n = 108) or placebo (n = 48). In the intention-to-treat population, 57.4% of isotretinoin recipients reached the primary endpoint, compared with 10.4% of those taking the placebo (absolute difference, 47 percentage

				points; 95% confidence interval, 34.3-59.7; P < 0.0001). To consider therapy successful, 2.1 (95% confidence interval 1.7-2.9) patients had to be treated. Skindex scores had improved significantly more for isotretinoin- than placebo-treated patients. Rosacea relapsed in 27 (58.3%) of 51 patients who accepted 4 months of continued follow-up, with a median of 15 weeks to recurrence. The percentages of patients in each arm who stopped their treatment because of adverse event(s) did not differ. Low-dose isotretinoin was an effective therapeutic option for difficult-to-treat papulopustular rosacea.
Shemer, et al.[11] (2021)	Canada	Retrospective study	77 patients	Forty milligrams per week isotretinoin was highly effective for severe rosacea, achieving complete response (over 90% improvement) in 62.5% of patients and partial response (50%-90% improvement) in additional 29.2% of patients. Twenty milligrams per week isotretinoin and hundred milligrams per day minocycline showed comparable efficacy for mild to moderate rosacea (complete response of 10.7% vs 8.3% and partial response of 28.6% vs 33.3%, respectively). This study demonstrates that that the use of a weekly low-dose isotretinoin is an effective treatment for papulopustular rosacea,

				including among patients with severe disease.
Kwon, et al.[12] (2020)	Korea	Retrospective study	25 patients	At the final follow-up visit, the number of papules and pustules decreased by 71%, and erythema index by 54% compared with baseline ($P < 0.05$ for both). Physician's global assessment based on rosacea severity score and patients' subjective assessments paralleled with these results. No serious side effect was observed during whole study periods.
Rademaker, et al.[13] (2018)	New Zealand	Retrospective study	52 patients	Altogether 52 patients (33 women), mean age 48 years (range 18-86) were treated with isotretinoin over a 5-year period. All patients were commenced on 20-mg isotretinoin/day which was reduced to 10-20 mg once to five times a week (equivalent to 5 mg/day) in 67%, but increased in 15% (who all had additional acne) to 30-40 mg/day. In terms of dose/kg/day, 29% received ≤ 0.1 mg/kg/day, 46% received 0.11-0.25 mg/kg/day and 10% received > 0.5 mg/kg/day. Treatment was continued for 57 weeks (range 9-223). Six patients (12%) did not attend follow up. Of the remainder, in 91% (42/46) the rosacea had cleared or was excellent.

				One patient stopped isotretinoin because of its adverse effects. Two-fifths (44%) suffered no adverse effect. The most common side-effect was cheilitis in half (52%), which was mild in all but one patient.

DISCUSSION

Current evidence demonstrates that low-dose isotretinoin (LDI) is an effective treatment for rosacea, particularly due to its immunomodulatory, anti-inflammatory, and anti-angiogenic properties. The mechanism of action of isotretinoin in rosacea is thought to be linked to its ability to reduce sebocyte proliferation, thereby decreasing the production of sebum, which plays a significant role in improving rosacea symptoms. Additionally, isotretinoin has been shown to alter the skin microbiome, including effects on Cutibacterium acnes and Malassezia species, though its impact on Demodex folliculorum—a common skin mite associated with rosacea—is less understood. Studies suggest that isotretinoin reduces Demodex density in skin explants, showing promise in this aspect of rosacea management.[9]

Despite its efficacy, the use of isotretinoin in treating rosacea has been largely limited to severe cases. This is partly due to its potential adverse effects, lack of formal approval for rosacea treatment by regulatory agencies, and the need for strict pregnancy monitoring in women of childbearing age, given the drug's teratogenic risks. Nevertheless, the adverse event rate for LDI in rosacea treatment is low, with only 0.36% of patients experiencing significant adverse effects, all of which were resolved either by reducing the dose or stopping the medication. This suggests that LDI offers a safer option for patients by achieving clinical improvement in rosacea while minimizing negative impacts on their quality of life.[10]

LDI has been shown to be particularly effective for cutaneous manifestations of rosacea, outperforming oral tetracycline in reducing lesion count and erythema. For ocular rosacea and related conditions such as meibomian gland dysfunction (MGD), oral doxycycline remains more effective, but LDI still presents a viable option. Studies found no significant difference between LDI and oral doxycycline in terms of visual outcomes or dryness measures, and low doses of isotretinoin (5–20 mg/day) were generally well-tolerated, even in patients with pre-existing ocular dryness.[11]

A major limitation of current studies on LDI for rosacea is the variation in outcome measurement tools, making it difficult to compare findings across studies comprehensively. In addition, the studies included in analyses ranged in quality, with some concerns regarding potential biases in study design and reporting. Despite this, all studies reported symptom improvement with LDI, and the rates of adverse events and relapses were consistent across studies, reinforcing the potential benefits of LDI for rosacea management.[12]

Another key point is the lack of a standardized definition of erythema across studies, which may affect the interpretation of improvements in this symptom. Future research should focus on differentiating the effects of LDI on various types of erythema, such as perilesional, persistent, and transient flushing erythema. Given that LDI is only suspensive in rosacea, mid-term maintenance therapy also warrants further investigation through randomized controlled trials to better understand how LDI can be integrated into long-term rosacea management strategies.[13]

CONCLUSION

Low-dose isotretinoin is an effective treatment for moderate-to-severe or recalcitrant rosacea. All studies reviewed indicate that LDI improves symptoms with generally mild, dose-dependent side effects. LDI should be considered a valuable therapeutic option for rosacea, especially for patients who do not respond to traditional treatments.

DISCLOSURE STATEMENT

Disclosure Statement : The authors have no conflicts of Interest to declare.

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