



## Review

# The use of isotretinoin increases the risk of inflammatory bowel disease. A narrative review

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### ABSTRACT

**Introduction:** Acne vulgaris represents a prevalent dermatological condition capable of exerting a profound impact on an individual's quality of life. Isotretinoin, despite its well-established status as a highly effective remedy for severe acne, concerns surrounding the potential linkage with inflammatory bowel disease (IBD) have led to inquiries about its association.

**Objective:** The primary objective of this review is to critically assess the existing body of evidence pertaining to the efficacy and safety of isotretinoin, with a particular emphasis on its association with IBD.

**Methods:** A literature review was undertaken to examine the utilization of isotretinoin in the management of acne and to evaluate the subsequent risk of inflammatory bowel disease, aiming to determine the relevance of considering this factor when utilizing this treatment.

**Conclusions:** Isotretinoin is widely recognized as the most effective therapeutic approach to treat acne. This compound competently addresses all underlying factors contributing to acne pathogenesis. Over time, extensive deliberation has arisen concerning concerns related to its potential correlation with the onset of IBD. The currently available evidence conveys a paucity of substantial scientific support for a causal relationship between the use of isotretinoin and the development of IBD.

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# El uso de isotretinoína aumenta el riesgo de enfermedad inflamatoria intestinal. Una revisión narrativa

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## RESUMEN

**Introducción:** El acné vulgaris representa una afección dermatológica prevalente capaz de ejercer un profundo impacto en la calidad de vida de un individuo. La isotretinoína, a pesar de su estatus bien establecido como un fármaco altamente efectivo para el acné severo, las preocupaciones en torno a la posible asociación con la enfermedad inflamatoria intestinal (EII) han llevado a investigaciones sobre su seguridad.

**Objetivo:** El objetivo principal de esta revisión es evaluar de manera crítica el cuerpo existente de evidencia relacionada con la eficacia y seguridad de la isotretinoína, con un énfasis particular en su asociación con la EII.

**Métodos:** Se realizó una revisión de la literatura para examinar la utilización de la isotretinoína en el tratamiento del acné y evaluar el riesgo subsiguiente de enfermedad inflamatoria intestinal, con el objetivo de determinar la relevancia de considerar este factor al utilizar este tratamiento.

**Conclusiones:** La isotretinoína es ampliamente reconocida como el enfoque terapéutico más efectivo para tratar el acné. Este compuesto aborda de manera competente todos los factores subyacentes que contribuyen a la patogénesis del acné. Con el tiempo, ha surgido una extensa deliberación con respecto a preocupaciones relacionadas con su posible correlación con el inicio de la EII. La evidencia científica actualmente disponible muestra un vacío significativo, que respalde un vínculo causal entre el uso de la isotretinoína y la aparición de la EII.

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## 1. INTRODUCTION

Acne is a chronic inflammatory dermatological condition that affects the pilosebaceous unit, which includes the hair follicle, hair shaft, and sebaceous gland [1]. Globally, around 650 million people suffer from acne, with higher prevalence in regions such as Western Europe, North America, and South America [2]. This condition predominantly manifests during adolescence, affecting over 95% of adolescent males and approximately 85% of adolescent females [3, 4]. In the United States, it is estimated that 85% of individuals aged 12 to 25-experience acne [5-7].

The pathogenesis of acne involves a complex interplay of factors including androgen-induced stimulation of sebaceous glands, alterations in the pilosebaceous follicle microbiome, and innate and cellular immune responses [8, 9]. Key pathogenic factors include follicular hyperkeratinization, increased sebum production, the presence of *Cutibacterium acnes*, and inflammation [10, 11]. Androgens play a crucial role in acne development by promoting the growth and activity of sebaceous glands, leading to increased sebum production that creates an

environment conducive to *C. acnes*. Immune responses to *C. acnes* contribute to inflammation and lesion formation [12]. Genetic predisposition also influences acne severity and variability in immune response and bacterial strains [13, 14]. Treatment of acne should be tailored to the specific pathophysiology and patient characteristics, as summarized in Table 1, which outlines various treatment modalities and their mechanisms of action [15]. Hormonal treatments are considered for cases of hyperandrogenism, late-onset acne, perimenstrual exacerbations, or resistance to other therapies [16]. Oral contraceptives work by reducing androgen production through suppression of luteinizing hormone (LH), increasing sex hormone-binding globulin (SHBG) to lower free testosterone, inhibiting 5-alpha reductase activity, and blocking androgen receptors to mitigate androgen effects. Table 2 lists the most common antiandrogenic combinations used in these treatments [16]. Antibiotic treatments, including tetracyclines, are also outlined in Table 3, typically used at non-antimicrobial doses [17]. For severe acne, isotretinoin is often recommended, particularly for cases involving nodules, cysts, or inflammatory acne with a high risk of scarring [18]. However, concerns about isotretinoin's side effects, including its potential association with Inflammatory Bowel

Disease (IBD), have prompted further research [19]. The aim of this review is to critically assess the available evidence regarding the efficacy and safety of isotretinoin, with a particular focus on its relationship with IBD.

harbor the potential to induce permanent scarring. Consequently, isotretinoin emerges as a viable alternative when initial treatments prove unproductive [21]. The mode of action of isotretinoin exhibits a distinct

**Table 1: Treatment according to pathophysiology**

Pathophysiology	Treatment
<b>Follicular hyperkeratinization</b>	Topical retinoids, oral isotretinoin, azelaic acid, salicylic acid
<b>Increased sebum production</b>	Oral isotretinoin, anticonceptivos orales, espironolactona
<b>Follicular colonization by <i>Cutibacterium acnes</i></b>	Benzoyl peroxide, topical and oral antibiotics, azelaic acid
<b>Inflammation</b>	Oral isotretinoin, oral tetracyclines, topical retinoids, azelaic acid.

## 2. ISOTRETINOIN IN THE MANAGEMENT OF ACNE

Isotretinoin, also referred to as 13-cis-retinoic acid, constitutes a naturally occurring derivative of vitamin A. Formulations for its application are available in both topical and oral forms. In 1982, the United States Food and Drug Administration granted the approval for oral isotretinoin in treating nodulocystic acne. Subsequently, in 1983, its usage also garnered the endorsement of the European Medicines Agency (EMA). Since then, the lives of numerous acne patients have been significantly enhanced by isotretinoin [20].

**Table 2: Antiandrogenic combinations**

Dienogest (2mg) + ethinyl estradiol (30mcg)
Cyproterone acetate (2 mg) + ethinyl estradiol (20-35 mcg)
Drospirenone (3 mg) + ethinyl estradiol (20 mcg)
Chlormadinone acetate (2 mg) + ethinyl estradiol (30 mcg)

Across time, isotretinoin has brought about a transformation in the realm of acne therapy and continues to be acknowledged by the medical community as the most clinically effective anti-acne treatment. According to the European guidelines, the indications for the utilization of oral isotretinoin encompass severe acne manifestations, specifically nodular and conglobate presentations, regardless of responses to prior treatments. It is the primary preference for individuals contending with severe forms of acne, including cystic and nodular phenotypes, as well as any type of acne linked to active scarring. It is imperative to underscore that all acne lesions, not solely cysts and nodules,

capacity to address comprehensively all fundamental factors contributing to the onset of acne. It results in a notable reduction in the production of sebum and the dimensions of sebaceous glands, which yields effective suppression of *Propionibacterium acnes* and a concomitant reduction in inflammation associated with acne [22].

Generally, isotretinoin is administered at a daily dosage ranging from 0.5 to 1.0 mg/kg of body weight, with most patients experiencing substantial improvements within a span of 16 weeks [23]. The consumption of isotretinoin with a fatty meal is advisable to optimize its absorption. In situations of severe acne, initial doses of a lesser magnitude may be employed alongside oral corticosteroids to mitigate the risk of severe outbreaks and scarring, a condition known as fulminant pseud acne. Typically, the objective is to reach a cumulative dosage within the range of 120 to 150 mg/kg over a period of 4 to 6 months to curtail the likelihood of relapses [24].

Nonetheless, prior to treatment initiation, the performance of laboratory tests becomes imperative, encompassing lipid profiles and liver function assessments. These evaluations must be executed both at the onset of therapy and approximately in the second month, particularly as the maximum daily dosage is attained. Significantly, heightened triglyceride levels emerge as the laboratory abnormality most frequently detected in isotretinoin-treated patients, with normalization typically ensuing upon completion of treatment [25].

Isotretinoin is associated with several potential side effects, including dryness of the lips, skin, and eyes. Elevations in liver enzyme levels are a commonly observed occurrence, which typically revert to baseline upon treatment cessation. Less frequent side effects encompass headaches and joint

**Table 3: Antibiotic treatment**

Group	Antibiotic
<b>Tetracycline</b>	Doxycycline (100 mg) Minocycline (100 mg) Lymecycline (300 mg)
<b>Others</b>	Trimethoprim sulfamethoxazole (160/800 mg) Azithromycin (500 mg)

and muscle discomfort, which are generally manageable. Although initial concerns regarding psychiatric side effects existed, current evidence suggests an uncertain and controversial connection between isotretinoin and psychiatric issues [26].

### 3. IS THERE A RELATIONSHIP BETWEEN THE USE OF ISOTRETINOIN AND INFLAMMATORY BOWEL DISEASE?

The potential relationship between isotretinoin and IBD, encompassing both Crohn's disease and ulcerative colitis, has been the subject of continuous debate, supported by limited evidence. Guidelines issued by the U.S. working group in 2016 assert that the current evidence is insufficient to confirm an association or causal link between isotretinoin and IBD [27]. Canadian guidelines provide some information based on studies regarding the potential correlation between isotretinoin and IBD development. They suggest that before initiating isotretinoin treatment, it would be advisable to inquire about IBD symptoms and assess relevant family history while addressing the ongoing debate on this matter. However, these guidelines do not provide a conclusive recommendation on the subject [28]. In contrast, European S3 guidelines do not offer specific recommendations concerning the relationship between oral

isotretinoin and IBD [29].

Considering the most robust and currently available information, a comprehensive analysis of the risk of developing IBD associated with isotretinoin was conducted through a meta-analysis encompassing studies published up to July 2015 [30].

In parallel, in a comprehensive systematic review conducted by Cochrane, the effectiveness and safety of oral isotretinoin as an acne treatment were assessed based on the best available evidence [31]. This review, which comprised 26 RCTs, did not report any cases of IBD. In addition to the RCTs, supplementary searches for non-RCT related to adverse effects were conducted, and the references of the RCTs were reviewed, leading to the identification of six non-RCT investigating the relationship between oral isotretinoin and the risk of IBD. Among these studies, Crockett et al. [32] identified a significant association between oral isotretinoin and ulcerative colitis (though not with Crohn's disease), while Alhusayen et al. [33] found a link between oral isotretinoin and IBD in participants aged 12 to 19, but only within a predefined age range subgroup. In contrast, the other four studies [34-37] did not reveal an increased incidence of IBD in relation to oral isotretinoin use. In 2014, Rashtak et al. [35] found even a reduction in the risk of IBD associated with isotretinoin exposure, and Racine et al. [37] identified that isotretinoin use was linked to a reduced risk of ulcerative colitis. It is important to note

**Table 4: Summary of Studies on Isotretinoin and Inflammatory Bowel Disease (IBD)**

Study	Type of study	Key findings	Conclusions
Lee SY et al. [30]	Systematic review and meta-analysis (2 retrospective cohort studies, 4 case-control studies; n = 9,724,069)	No statistically significant risk of developing IBD associated with isotretinoin (OR 1.08; 95% CI: 0.82-1.42; p = 0.59).	No increased risk for Crohn's disease or ulcerative colitis.
Costa CS et al. [31]	Systematic review and meta-analysis (26 RCTs)	No cases of IBD reported in RCTs. Additional searches identified 6 non-RCTs; mixed results, with some studies showing an association and others not.	Mixed evidence; no consistent association found.
Yu CL et al. [38]	Systematic review and meta-analysis (8 studies, n = 2,522,422)	No increased odds for IBD (OR 1.01; 95% CI 0.80-1.27), Crohn's disease (OR 0.87; 95% CI 0.65-1.15), or ulcerative colitis (OR 1.27; 95% CI 0.94-1.73) associated with isotretinoin.	No evidence to withhold isotretinoin due to concerns for IBD.
Crockett et al. [32]	Case-control study	Significant association between isotretinoin and ulcerative colitis, but not Crohn's disease.	Suggests a potential risk for ulcerative colitis.
Alhusayen et al. [33]	Retrospective population-based cohort	Association between isotretinoin and IBD in participants aged 12-19, but only within a specific age subgroup.	Possible age-related risk.
Rashtak et al. [35]	Retrospective, single-center study	Found a reduction in the risk of IBD associated with isotretinoin exposure.	Suggests a protective effect against IBD.
Racine et al. [37]	Nationwide case-control study	Identified a reduced risk of ulcerative colitis associated with isotretinoin use.	Suggests a protective effect against ulcerative colitis.

that there was no assessment of bias risk or evaluation of the quality of evidence in these studies related to oral isotretinoin and IBD. Additionally, it is reported that no reports of serious adverse effects were found in other non-RCT reviewed during the additional selection process.

The most recent systematic review and meta-analysis, which included eight studies (four case-control and four cohort studies) with a total of 2,522,422 participants found no increased odds for IBD among patients receiving isotretinoin (OR 1.01; 95% confidence interval [CI] 0.80-1.27). Nor did the meta-analysis find increased odds for either Crohn disease (OR 0.87; 95% CI 0.65-1.15) or ulcerative colitis (OR 1.27; 95% CI 0.94-1.73) associated with isotretinoin exposure. The sensitivity and subgroup analyses produced similar results. In TSA, the Z-curve reached the futility boundaries when using relative risk reduction thresholds ranging from 5% to 15% and argues that Isotretinoin should not be withheld because of unnecessary concerns for the development of IBD [38]. Finally, reviewing other articles, they also maintain that there is not a consistent association between isotretinoin use and risk of inflammatory bowel disease. There is no clear evidence of a causal link [39-41]. See Table 4 for a summary of these studies.

#### 4. CONCLUSIONS

Acne is a multifaceted dermatological condition that necessitates a tailored approach to treatment. Various therapeutic options are available, with isotretinoin emerging as a highly effective treatment for severe cases, particularly nodular and conglobate forms, along with any acne types associated with active scarring. It stands out as the sole therapy addressing all critical factors contributing to acne development. When considering isotretinoin therapy, healthcare professionals should conduct a comprehensive evaluation of each patient's medical history and assess the severity of their acne. Treatment should be individualized, and potential risks must be carefully weighed. Monitoring for adverse effects should be continuous throughout the treatment period.

Based on the most rigorous and up-to-date scientific evidence, it is evident that concerns regarding the potential causal association between isotretinoin use and IBD lack substantial scientific support. The prevailing data strongly suggests that the advantages of utilizing isotretinoin in the treatment of severe acne far surpass the risk of IBD onset. Furthermore, isotretinoin remains a pivotal component in the management of severe acne, markedly enhancing the quality of life for numerous individuals grappling with this

condition. Overall, isotretinoin continues to play a crucial role in the management of severe acne, significantly improving the quality of life for many individuals affected by this condition. Patient-specific assessments and ongoing monitoring are essential to ensure the safe and effective use of this medication.

#### 5. CONFLICT OF INTERESTS

The authors have no conflict of interest to declare. The authors declared that this study has received no financial support.

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