TYLCZYŃSKA, Kinga, TYLCZYŃSKA, Natalia, SKIBA, Jakub, SKIBA, Zuzanna, KOWALIK, Kinga, MICHALSKA, Maria, ZIELIŃSKA, Aleksandra, SZYPULSKI, Szymon, IWANIUK, Sebastian and MACIEJEWSKI, Ignacy. Outcomes and Adverse Effects of Isotretinoin in Acne Treatment: A Systematic Review. Quality in Sport. 2024;33:56178 eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.33.56178
https://apcz.umk.pl/QS/article/view/56178

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assig589 ned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 13.11.2024. Revised: 20.11.2024. Accepted: 27.11.2024. Published: 27.11.2024.

Outcomes and Adverse Effects of Isotretinoin in Acne Treatment: A Systematic Review

Authors
Kinga Tylczyńska
Orcid: https://orcid.org/0009-0008-1820-3013
email: kinga0799@gmail.com
Cardinal Stefan Wyszynski University in Warsaw, Kazimierza Wóycickiego 1/3, 01-938 Warsaw, Poland

Natalia Tylczyńska
Orcid: https://orcid.org/0009-0002-8668-0272
email: nataliat0206@gmail.com
Cardinal Stefan Wyszynski University in Warsaw, Kazimierza Wóycickiego 1/3, 01-938 Warsaw, Poland

Jakub Skiba
Orcid: https://orcid.org/0009-0002-2451-6477
email: jakubskiba@onet.pl
Independent Public Health Care Facility in Koło, Księcia Józefa Poniatowskiego 25, 62-600 Koło, Poland

Zuzanna Skiba
Orcid: https://orcid.org/0009-0001-7583-5868
email: zskiba42@gmail.com
Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

Kinga Kowalik
Orcid: https://orcid.org/0009-0000-4894-6987
email: k_kowalik@outlook.com
Wolski Hospital, Marcina Kasprzaka 17, 01-211 Warsaw, Poland

Maria Michalska
Orcid: https://orcid.org/0009-0004-7822-8299
email: michalskamaria209@gmail.com
Wolski Hospital, Marcina Kasprzaka 17, 01-211 Warsaw, Poland

Aleksandra Zielińska
Orcid: https://orcid.org/0009-0007-4791-9160
email: olazielinska2217@gmail.com
Praski Hospital in Warsaw, al. „Solidarności" 67, 03-401 Warsaw, Poland

Szymon Szypulski
Orcid: https://orcid.org/0009-0008-7228-7086
email: szymon.szypulski2803@gmail.com
Infant Jesus Teaching Hospital, Williama Heerleina Lindleya 4, 02-005 Warsaw, Poland

Sebastian Iwaniuk
Orcid: https://orcid.org/0009-0000-9125-6172
email: sebastian.iwaniuk@icloud.com
University Clinical Centre of the Medical University of Warsaw, ul. Banacha 1A, 02-097 Warsaw, Poland

Ignacy Maciejewski
Orcid: https://orcid.org/0000-0002-0424-9095
email: ignacy.3.11@gmail.com
5th Military Clinical Hospital in Cracow, Wrocławska 1/3, 30-901 Cracow, Poland

Abstract

Introduction and purpose: Isotretinoin (13-cis-Retinoic Acid), is a drug for moderate to severe acne that doesn't respond to other treatments. The purpose of this review was to present the mechanism of action, outcomes and adverse effects of isotretinoin.

Description of state of knowledge: Isotretinoin is a very lipophilic drug and is used in dermatology to treat acne vulgaris due to its inhibitory effect on sebaceous gland activity and

proliferation. Isotretinoin can cause side effects across various body systems. Extra caution is advised for patients with lipid abnormalities or impaired liver function.
For women of reproductive age, it's crucial to use contraception starting one month before, throughout, and for one month after isotretinoin treatment due to teratogenicity.
Conclusions: Oral isotretinoin is a highly effective acne treatment that helps prevent both physical scarring and psychological impacts associated with severe acne. Although generally associated with mild and reversible side effects, isotretinoin is teratogenic, which requires careful patient management.

Keywords: isotretinoin, acne vulgaris, adverse effects, retinoids

1. Introduction and purpose

Acne is a long-lasting, inflammatory condition driven by the immune system that affects the pilosebaceous units. It typically starts during puberty when the production of sex hormones begins [1]. Interactions between the host and microbiome that influence both innate and adaptive immune balance seem to play a crucial role in this condition. Recent findings indicate that the composition and activity of the microbiota in acne are disrupted [2]. Acne is highly common among adolescents, but it can develop at any age. It is considered one of the top three most common skin conditions encountered in dermatology consultations [3]. Acne involves the face, trunk, and back with inflammatory lesions that may evolve to scars. Proper, early, effective, and safe treatment is essential for achieving disease remission without any physical or emotional aftereffects. Various topical products are available for treating acne, along with three systemic treatment options: antibiotics, antiandrogens (such as combined oral contraceptives and spironolactone), and isotretinoin. Additional procedures can also be used to complement these treatments [4]. The treatment typically needs to be extended over a long period, and ongoing maintenance therapy is often required [5].

Isotretinoin, also known as 13-*cis*-retinoic acid is now an increasingly popular and most effective form for patients with moderate acne who fail to respond to other forms of treatment e.g. antibiotics and should be indicated early, when planning treatment, to prevent psychosocial impact and scars [6]. It is more and more often considered the only chance for the patient to regain health. Isotretinoin is the only one that affects most of the factors that cause acne. It is a retinoid, a compound related to vitamin A, and is naturally present in the body in small amounts. Its efficacy has been established over the past 42 years through numerous publications, including systematic reviews and meta-analyses [7]. Oral isotretinoin effectively suppresses sebaceous gland activity through multiple pathways and also possesses anti-inflammatory and immunomodulatory effects by down-regulating TLR 2 and 4 receptors and Th cells [8]. The label recommended daily dose is 0.5–1.0 mg/kg up to the total of 120–150 mg/kg. Manageable and reversible side effects, including mucocutaneous reactions and alterations in laboratory tests such as lipid profiles and liver transaminases, may occur. Women in childbearing age must be especially careful and use at least two reliable and safe contraceptives and have their beta hCG measured monthly, because one of the most serious, irreversible and dose-independent side effects of isotretinoin is teratogenicity [9,10]. Many publications have pointed out that this drug has more benefits, namely patients see more

improvement and cure, than there is a risk of complications, such as depressive symptoms which are related to acne [11]. It is recommended to laboratory monitor serum lipids and liver transaminases before treatment and after four to six weeks, with reevaluations for the altered results [12].

Since its introduction, 42 years have passed and the drug continues to be highly effective. Its use has never been discontinued, despite the fact that few countries have not yet approved it [13].

2. The pathophysiology of acne

Acne affects 80–90% of teenagers between the ages of 16 and 20. A population-based study in five European countries reported an acne prevalence rate of 19.2%. The study also found that women are more likely to be affected by acne than men [3]. The pathogenesis of acne is complex and not fully understood. Key factors are: genetic predisposition, the role of sebaceous glands as the central affected skin structure with receptors in sebocytes, conversion of testosterone to dihydrotestosterone (DHT), local or intracrine androgen production, and changes in sebum composition [14]. DHT activates sebocytes by binding to its nuclear receptor, leading to the production of sebum that differs in composition compared to that of normal skin. Acne-prone skin shows increased activity of *Cutibacterium acnes*, recognized by Toll-like receptors (TLR 2 and 4) in skin cells, triggering inflammation. Follicular hyperkeratinization is influenced by androgens and cytokines, and the presence of neuropeptide receptors in sebocytes suggests stress also affects acne development. Inflammation triggered by multiple pathways is the primary and earliest factor in the development of acne, occurring even before visible lesions appear [15]. *C. acnes* plays a role in the immune response by stimulating the release of antimicrobial peptides from sebocytes and keratinocytes and promoting the Th17 immune response [16]. Acne treatment options include skincare guidance (cosmeceuticals such as cleansers, moisturizers, sunscreens, and makeup for women), topical medications (like benzoyl peroxide, tretinoin, adapalene, azelaic acid, fixed combinations, and new emerging agents), systemic drugs, and additional procedures (such as chemical peels, lasers, and light therapies). Typically, a combination of topical and systemic therapies is needed, except in mild cases or when oral isotretinoin is prescribed [4]. Besides antiandrogens and isotretinoin, systemic treatments are mainly limited to antibiotics, particularly from the tetracycline class. However, their use is increasingly discouraged due to the rising issue of bacterial resistance [17].

3. Mechanism of an action

Oral isotretinoin, an isomer of all-trans retinoic acid, belongs to the first generation of retinoids. Isotretinoin is a treatment for severe cases of acne due to its ability to reduce sebaceous gland size, inhibit sebum production, and modulate skin cell turnover, leading to a significant reduction in acne lesions [18]. The first generation of retinoids, including isotretinoin, is characterized by a chemical structure that retains the cyclic chain of vitamin A. These modifications enhance the molecule's lipophilicity, which in turn improves its bioavailability [19]. Retinoids exert their effects by interacting with nuclear retinoic acid receptors (RARs), which are ligand-dependent transcription factors. This means that gene

transcription is regulated only when a compound binds to the receptor. However isotretinoin has a low affinity for retinoic acid receptors (RARs) and retinoid X receptors (RXRs), functioning as a prodrug that requires conversion intracellulary into active metabolites such as all-trans retinoic acid (ATRA). These metabolites bind to retinoid receptors to exert their effects and modulate the expression of various genes, influencing multiple cellular processes by either upregulating or downregulating gene activity [20, 21].

Isotretinoin targets four primary factors involved in acne pathogenesis: it normalizes follicular desquamation, decreases sebum production, inhibits the growth of Cutibacterium acnes, and exhibits anti-inflammatory properties. Research suggests that these anti-acne effects are largely due to isotretinoin-induced apoptosis of sebocytes and other skin cells [22, 23]. At the molecular level, isotretinoin and its metabolites help to correct follicular hyperkeratinization by modulating the expression of specific proteins. It reduces the production of cytokeratins 1, 10, and 14, as well as filaggrin and matrix metalloproteinases (MMPs). Conversely, it increases the levels of cytokeratins 7, 13, and 19, laminin B1, and interleukin-1 (IL-1). These changes result in decreased adhesion of corneodesmosomes and corneocytes, which promotes cellular turnover and renewal within hair follicles, effectively reducing comedone formation and inflammation [24]. Furthermore, isotretinoin can impact human lipid metabolism by significantly decreasing sebum production while simultaneously raising blood lipid levels. The sebum-suppressive effect of isotretinoin is linked to the induction of sebocyte apoptosis through isotretinoin-mediated p21-induced cell cycle arrest and the upregulation of pro-apoptotic transcription factors [25]. Isotretinoin stimulates the expression of the p53 gene, which plays a central role in regulating various cellular signaling pathways, including those involved in apoptosis and lipogenesis. The inhibition of the IGF-1R/PI3K/AKT/mTORC1 and PPAR-γ pathways leads to a reduction in sebaceous gland lipogenesis [26]. Isotretinoin circulates in the bloodstream, where it is metabolized by the liver and then excreted via the bile ducts or the kidneys. Retinoid-binding proteins, which help stabilize retinoids in aqueous environments, include plasma Retinol-Binding Proteins (RBPs), Cellular Retinoid Binding Proteins (CRBP I, II, III, and IV), and Cellular Retinoic Acid Binding Proteins (CRABP I and II). Synthesized in the liver, RBPs transport vitamin A to target tissues. The retinol-protein complex helps stabilize retinoids and prevents their filtration through the renal glomerulus [27].

4. Efficacy and optimal dosing

The first guidelines for optimal use of isotretinoin for acne were published in 1992. Oral isotretinoin is a safe and the most effective option for acne treatment, despite common and easily controlled side effects. Teratogenicity and clinical and laboratory parameters such as AST and ALT must be strictly controlled. It is the only drug to be used as monotherapy, because it acts against all currently known factors related to acne pathogenesis [7]. The original indication of isotretinoin for treating severe nodular-cystic acne has been expanded to include moderate papulo-pustular acne that is unresponsive to previous treatments, tends to scar, or has a negative psychosocial impact. If there are no formal contraindications, this medication should be initiated early to help achieve acne remission and prevent long-term consequences [6, 20]. Significant improvements can often be seen within the first two to three

months of treatment. The standard and approved daily dosage, as recommended by health regulatory authorities, ranges from 0.5 to 1.0 mg/kg, with a cumulative dose of 120–150 mg/kg. The medication should be taken after meals to enhance absorption due to its lipophilic nature [7]. Recurrence rates reported in studies vary significantly, ranging from 5% to 65%, depending on factors such as the duration of follow-up and the size of the study sample. Recurrences tend to present as milder forms of the disease, which can be managed with topical treatments [28]. A systematic review, published in 2018, analyzed studies with different daily dose and therapeutic regimen [7].

The efficacy was better when the conventional or low dose was used (<0.5 mg/kg) every day compared to alternate days or intermittent scheme (one week, once a month). The latter is less effective and is not recommended. Mild adverse events were more frequent with continuous daily use. The treatment duration can be extended, sometimes lasting up to 18 months, particularly in cases of severe acne or when acne occurs outside of the face [12]. Recent studies suggest that relapses often occur when treatment is stopped after reaching the cumulative dose of 120–150 mg/kg, even though active lesions are still present. This indicates disease persistence rather than a true recurrence. Experts recommend a "gold rule" for treatment: continue until all lesions have completely resolved, and then extend the therapy for an additional one to two months to ensure long-term remission [13]. Then patients must continue maintenance treatment with topical medications for 6-12 months to ensure that the disease does not return [5].

5. Relapse

The significant factors for relapse include stopping isotretinoin before acne has cleared completely, macrocomedonal disease, severity of acne, excessive seborrhoea after finishing isotretinoin, smoking, younger age (under 14), older age (women over 25), polycystic ovarian syndrome [13].

6. Surveillance and adverse effects

All treated patients suffer from side effects. The range and severity of the side effects depends on the disease being treated, the dose of isotretinoin and personal factors.

6.1. Mucocutaneous

Common and relatively mild side effects of oral isotretinoin, affecting around 90% of patients, include dryness of the skin and mucous membranes. This occurs due to a reduction in sebum production, thinning of the stratum corneum, and alterations in the skin barrier function. The most common side effects related to the skin and mucous membranes are: cheilitis (90–100% of patients), cutaneous xerosis, erythema, pruritus, desquamation, dryness of nasal mucosa, epistaxis, worsening or triggering atopic dermatitis, telogen effluvium, dry eyes, and inflammation of the eyelids. These symptoms are reversible, controllable, predictable and dose-dependent. To prevent these common side effects, it is necessary to start using gentle cleansers, moisturizers, and lubricants for the lips, eyes, and nasal mucosa from the first day of treatment. Other potential adverse effects include headaches, hair loss (alopecia), joint pain (arthralgias), muscle pain (particularly in athletes), insomnia, and hyperostosis [7, 29].

6.2. Laboratory parameters

Laboratory abnormalities account for 2% of adverse events and include increases in triglycerides (44%), total and LDL cholesterol (33%), and transaminases (11%). These changes are typically mild or uncommon in healthy adolescents and generally occur early in the treatment. As a result, if monitoring is delayed, these alterations are unlikely to be detected [29, 30]. As a result, several retrospective studies support the recommendation for minimal pre-treatment testing, with follow-up tests repeated after 1–2 months. It is advised to check blood count, lipid profile, and transaminase levels.

This approach helps avoid unnecessary reevaluations, reducing both patient discomfort and overall costs. There are no long-term risks, as most adverse events are reversible, with the exception of teratogenicity. For mild alterations, reducing the dose is usually sufficient to restore normal values. However, if there is a threefold increase from the reference value, discontinuation of the treatment is recommended. The drug's impact on fatigue, muscle strength, and endurance has been previously studied, and no significant differences were observed in individuals taking isotretinoin. Therefore, CPK levels should only be measured when severe muscle pain is reported. Comorbidities or the emergence of side effect-related symptoms should guide personalized monitoring. Future genomic studies may shed light on the rare adverse events reported in case studies, which have fueled myths and controversies, leading to unwarranted bias against prescribing such an effective medication [12, 30].

6.3. Teratogenicity

As we mentioned earlier, the most serious side effect is teratogenicity. A possible reason for this is the increase of apoptosis of neural crest cells through overexpression of gene p53, which is a proapoptotic transcriptional factor [23, 31]. It is essential to conduct a pregnancy test before starting isotretinoin treatment and monthly thereafter, ensuring the patient awaits her menstrual period before beginning therapy. Additionally, two reliable contraceptive methods must be used during treatment and for one month after discontinuation. It’s important to note that there is no long-term risk to future pregnancies. However, while normal pregnancy outcomes occur in 65–85% of cases, there is a 10.9–20% risk of spontaneous abortion and a 18–28% risk of birth defects, typically involving craniofacial, thymus, and cardiovascular abnormalities [9, 10].

6.4. Acne flare-up

Severe inflammatory acne with extensive macrocomedones and a family history of the condition may experience an initial worsening within the first 8 weeks of treatment. This acne flare is triggered by intense sebocyte apoptosis, antigen release, and an inflammatory response, which resolves spontaneously in 15–18% of patients. However, it can resemble acne fulminans, presenting with intense inflammation, ulceration, crusting, and scarring but without systemic symptoms. To prevent this flare-up, it is recommended to begin isotretinoin at a low daily dose (0.1–0.2 mg/kg), combined with oral prednisone (0.5−1.0 mg/kg/day) for 2–4 weeks. The low dose should be maintained throughout the treatment, or at least for the

first 8 weeks, after which it may be gradually increased, depending on the patient's response, while tapering off the corticosteroid in a stepwise manner [32].

6.5. Musculoskeletal system

Isotretinoin can affect muscle and bone homeostasis when high daily doses (>1 mg/kg) are used over an extended period (>2 years) in children. However, the total dose used for acne treatment is much lower, so there is no significant risk of serious adverse effects on the musculoskeletal system, including premature epiphyseal closure, when treating acne [33].

6.6. Atypical tissue recovery

Cosmetic procedures like laser, microneedling, biopsies, and surgeries that don't reach the muscle layer can be safely performed. No increased risk of hypertrophic scars, keloids, or abnormal healing has been observed in patients using isotretinoin for less than 6 months or currently using it [34]. On the contrary, studies have shown that laser treatments are safe, and better outcomes can be achieved when combined with a low daily dose of isotretinoin (10 mg/kg) during the final month of treatment. Label recommendations suggest waiting six months after treatment before performing procedures like laser hair removal, dermabrasion, chemical peels, and surgical excisions. [35].

6.7. Psychiatric problems and depression

Various studies have never confirmed the increased risk of depression, suicide attempts and suicide. Treatment of acne with isotretinoin does not appear to be associated with an increased risk of depression. Moreover, acne treatment appears to alleviate depressive symptoms [36]. There is no psychiatric contraindication for isotretinoin.

6.8. Inflammatory bowel disease (IBD)

Systematic reviews and meta-analyses have shown no evidence of a link between oral isotretinoin and inflammatory bowel disease (IBD) [37]. However, an increased risk of IBD has been confirmed in acne patients, caused by the condition itself and/or the use of antibiotics, particularly tetracyclines [38]. Some evidence suggests that isotretinoin may even lower the risk of IBD, likely due to its anti-inflammatory and immunomodulatory effects, which help regulate the Th1/Th2 response balance and reduce excessive TLR expression [39].

6.9. Female infertility and reduced ovarian reserve

Isotretinoin does not affect ovarian function. It reduces hormone levels, but the results showed that they returned to normal. The possible effect on ovarian reserve was reversible [40].

6.10. Ophthalmologic side effects

Eye dryness, with or without conjunctivitis, can cause significant discomfort for contact lens users. The ocular side effects of isotretinoin include reduced ability to see in low light

(impaired dark adaptation), swelling of the optic nerve (papilledema), corneal changes like opacities, the development of cataracts, temporary episodes of acute myopia, and abnormal findings on electroretinogram tests. These adverse effects are typically reversible and usually subside within a month after stopping the medication [25].

7. Drug interactions

Using isotretinoin alongside alcohol or medications with similar side effects can raise the risk of adverse reactions. It is recommended to avoid [41]:

- Tetracyclines (such as doxycycline, minocycline, and tetracycline), which can increase the likelihood of headaches and blurred vision due to elevated intracranial pressure.
- Alcohol, which may exacerbate liver stress and lead to elevated blood lipid levels.

- Vitamin A supplements, since isotretinoin is a vitamin A derivative, and additional intake could result in toxicity, amplifying side effects like dry skin and mucous membrane irritation.

8. Final considerations

Based on reviews comparing total price of acne treatment using isotretinoin with long-term antibiotic therapy combined with topical treatments, it can be concluded that isotretinoin offers the best cost-to-benefit ratio. This is mainly because most patients taking isotretinoin are cured after just one course of treatment. However, the main downside of isotretinoin treatment is its duration, which ranges from six months to over 12 months. There is increasing concern about the growing antibiotic resistance associated with oral antibiotic use and the disregard for guidelines when prescribing them. It is also recommended to introduce isotretinoin as soon as other treatment options fail to produce results. The minimum age for taking the drug is not strictly defined, but in pre-adolescents, there may be a need for additional cycles of isotretinoin until the disease is cured. It is important to wait three months after completing one treatment cycle before starting a new one. The benefits of using a low daily dose of isotretinoin have also been documented, and this approach is becoming increasingly popular in treating acne and other dermatological conditions. Ultimately, the doctor's approach and building a strong relationship with the patient are key factors in ensuring the success of the treatment. It is essential for the doctor to inform the patient at the start of treatment about how isotretinoin works, what possible side effects to expect, and how to avoid them.

9. Summary

Acne is a chronic condition that predominantly affects adolescents, leading to inflammatory lesions on the face and trunk, which can potentially progress to scarring. The impact on quality of life is significant, with effects that can last a lifetime. The introduction of oral isotretinoin around 40 years ago revolutionized acne treatment, offering a way to clear the condition and prevent both physical scarring and psychological distress. This medication has been prescribed to millions of patients globally due to its high efficacy, despite the potential for adverse effects. Most side effects of isotretinoin are mild, reversible, and not severe, with

the exception of teratogenicity, which is the most serious concern. Other severe reactions are rare and often represent individual sensitivities similar to those seen with other medications. Given its effectiveness, early use of oral isotretinoin is recommended to prevent scarring and reduce the negative impact of acne on the lives of young people.

Disclosures

Author's contribution

Conceptualization - Kinga Tylczyńska and Natalia Tylczyńska; methodology - Jakub Skiba and Ignacy Maciejewski; software - Zuzanna Skiba and Sebastian Iwaniuk; check - Aleksandra Zielińska and Kinga Kowalik; formal analysis - Ignacy Maciejewski and Maria Michalska; investigation - Szymon Szypulski; resources - Natalia Tylczyńska; data curation - Jakub Skiba and Kinga Kowalik; writing - rough preparation - Maria Michalska and Aleksandra Zielińska; writing - review and editing - Sebastian Iwaniuk and Szymon Szypulski; visualization - Zuzanna Skiba; supervision - Kinga Tylczyńska; project administration - Kinga Tylczyńska; receiving funding not applicable. All authors have read and agreed with the published version of the manuscript.

Financing Statement

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article's bibliography.

Conflict of Interest

Authors declare no conflict of interest.

References:

1. Williams HC, Dellavalle RP, Garner S. Acne vulgaris [published correction appears in Lancet. 2012 Jan 28;379(9813):314]. *Lancet*. 2012;379(9813):361-372. doi:10.1016/S0140-6736(11)60321-8
2. O'Neill AM, Gallo RL. Host-microbiome interactions and recent progress into understanding the biology of acne vulgaris. *Microbiome*. 2018;6(1):177. Published 2018 Oct 2. doi:10.1186/s40168-018-0558-5
3. Svensson A, Ofenloch RF, Bruze M, et al. Prevalence of skin disease in a population-based sample of adults from five European countries. *Br J Dermatol*. 2018;178(5):1111-1118. doi:10.1111/bjd.16248
4. Thiboutot DM, Dréno B, Abanmi A, et al. Practical management of acne for clinicians: An international consensus from the Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol*. 2018;78(2 Suppl 1):S1-S23.e1. doi:10.1016/j.jaad.2017.09.078
5. Bettoli V, Borghi A, Zauli S, et al. Maintenance therapy for acne vulgaris: efficacy of a 12-month treatment with adapalene-benzoyl peroxide after oral isotretinoin and a review of the literature. *Dermatology*. 2013;227(2):97-102. doi:10.1159/000350820
6. Rigopoulos D, Larios G, Katsambas AD. The role of isotretinoin in acne therapy: why not as first-line therapy? facts and controversies. *Clin Dermatol*. 2010;28(1):24-30. doi:10.1016/j.clindermatol.2009.03.005
7. Costa CS, Bagatin E, Martimbianco ALC, et al. Oral isotretinoin for acne. *Cochrane Database Syst Rev*. 2018;11(11):CD009435. Published 2018 Nov 24. doi:10.1002/14651858.CD009435.pub2
8. Dispenza MC, Wolpert EB, Gilliland KL, et al. Systemic isotretinoin therapy normalizes exaggerated TLR-2-mediated innate immune responses in acne patients. *J Invest Dermatol*. 2012;132(9):2198-2205. doi:10.1038/jid.2012.111
9. Brzezinski P, Borowska K, Chiriac A, Smigielski J. Adverse effects of isotretinoin: A large, retrospective review. *Dermatol Ther*. 2017;30(4):10.1111/dth.12483. doi:10.1111/dth.12483
10. Tkachenko E, Singer S, Sharma P, Barbieri J, Mostaghimi A. US Food and Drug Administration Reports of Pregnancy and Pregnancy-Related Adverse Events Associated With Isotretinoin. *JAMA Dermatol*. 2019;155(10):1175-1179. doi:10.1001/jamadermatol.2019.1388
11. Li C, Chen J, Wang W, Ai M, Zhang Q, Kuang L. Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis [published correction appears in BMJ Open. 2019 Mar 15;9(3):e021549corr1. doi: 10.1136/bmjopen-2018-021549corr1]. *BMJ Open*. 2019;9(1):e021549. Published 2019 Jan 21. doi:10.1136/bmjopen-2018-021549
12. Lee YH, Scharnitz TP, Muscat J, Chen A, Gupta-Elera G, Kirby JS. Laboratory Monitoring During Isotretinoin Therapy for Acne: A Systematic Review and Meta-analysis [published correction appears in JAMA Dermatol. 2016 Jan;152(1):114. doi: 10.1001/jamadermatol.2015.6052]. *JAMA Dermatol*. 2016;152(1):35-44. doi:10.1001/jamadermatol.2015.3091

13. Rademaker M. Isotretinoin: dose, duration and relapse. What does 30 years of usage tell us?. *Australas J Dermatol*. 2013;54(3):157-162. doi:10.1111/j.1440-0960.2012.00947.x
14. Kurokawa I, Danby FW, Ju Q, et al. New developments in our understanding of acne pathogenesis and treatment. *Exp Dermatol*. 2009;18(10):821-832. doi:10.1111/j.1600-0625.2009.00890.x
15. Rocha MA, Costa CS, Bagatin E. Acne vulgaris: an inflammatory disease even before the onset of clinical lesions. *Inflamm Allergy Drug Targets*. 2014;13(3):162-167. doi:10.2174/1871528113666140606110024
16. Agak GW, Kao S, Ouyang K, et al. Phenotype and Antimicrobial Activity of Th17 Cells Induced by Propionibacterium acnes Strains Associated with Healthy and Acne Skin. *J Invest Dermatol*. 2018;138(2):316-324. doi:10.1016/j.jid.2017.07.842
17. Barbieri JS, Spaccarelli N, Margolis DJ, James WD. Approaches to limit systemic antibiotic use in acne: Systemic alternatives, emerging topical therapies, dietary modification, and laser and light-based treatments. *J Am Acad Dermatol*. 2019;80(2):538-549. doi:10.1016/j.jaad.2018.09.055
18. Khalil S, Bardawil T, Stephan C, et al. Retinoids: a journey from the molecular structures and mechanisms of action to clinical uses in dermatology and adverse effects. *J Dermatolog Treat*. 2017;28(8):684-696. doi:10.1080/09546634.2017.1309349
19. Mukherjee S, Date A, Patravale V, Korting HC, Roeder A, Weindl G. Retinoids in the treatment of skin aging: an overview of clinical efficacy and safety. *Clin Interv Aging*. 2006;1(4):327-348. doi:10.2147/ciia.2006.1.4.327
20. Larange A, Cheroutre H. Retinoic Acid and Retinoic Acid Receptors as Pleiotropic Modulators of the Immune System. *Annu Rev Immunol*. 2016;34:369-394. doi:10.1146/annurev-immunol-041015-055427
21. Nelson AM, Zhao W, Gilliland KL, Zaenglein AL, Liu W, Thiboutot DM. Isotretinoin temporally regulates distinct sets of genes in patient skin. *J Invest Dermatol*. 2009;129(4):1038-1042. doi:10.1038/jid.2008.338
22. Cruz S, Vecerek N, Elbuluk N. Targeting Inflammation in Acne: Current Treatments and Future Prospects. *Am J Clin Dermatol*. 2023;24(5):681-694. doi:10.1007/s40257-023-00789-1
23. Melnik BC. Apoptosis May Explain the Pharmacological Mode of Action and Adverse Effects of Isotretinoin, Including Teratogenicity. *Acta Derm Venereol*. 2017;97(2):173-181. doi:10.2340/00015555-2535
24. Törmä H. Regulation of keratin expression by retinoids. *Dermatoendocrinol*. 2011;3(3):136-140. doi:10.4161/derm.3.3.15026
25. Nelson AM, Gilliland KL, Cong Z, Thiboutot DM. 13-cis Retinoic acid induces apoptosis and cell cycle arrest in human SEB-1 sebocytes. *J Invest Dermatol*. 2006;126(10):2178-2189. doi:10.1038/sj.jid.5700289
26. Melnik BC. p53: key conductor of all anti-acne therapies. *J Transl Med*. 2017;15(1):195. Published 2017 Sep 19. doi:10.1186/s12967-017-1297-2

27. Zhang YR, Zhao YQ, Huang JF. Retinoid-binding proteins: similar protein architectures bind similar ligands via completely different ways. *PLoS One*. 2012;7(5):e36772. doi:10.1371/journal.pone.0036772
28. Leyden JJ, Del Rosso JQ, Baum EW. The use of isotretinoin in the treatment of acne vulgaris: clinical considerations and future directions. *J Clin Aesthet Dermatol*. 2014;7(2 Suppl):S3-S21.
29. Vallerand IA, Lewinson RT, Farris MS, et al. Efficacy and adverse events of oral isotretinoin for acne: a systematic review. *Br J Dermatol*. 2018;178(1):76-85. doi:10.1111/bjd.15668
30. Barbieri JS, Shin DB, Wang S, Margolis DJ, Takeshita J. The clinical utility of laboratory monitoring during isotretinoin therapy for acne and changes to monitoring practices over time. *J Am Acad Dermatol*. 2020;82(1):72-79. doi:10.1016/j.jaad.2019.06.025
31. Melnik BC. Overexpression of p53 explains isotretinoin's teratogenicity. *Exp Dermatol*. 2018;27(1):91-93. doi:10.1111/exd.13420
32. Borghi A, Mantovani L, Minghetti S, Virgili A, Bettoli V. Acute acne flare following isotretinoin administration: potential protective role of low starting dose. *Dermatology*. 2009;218(2):178-180. doi:10.1159/000182270
33. Tekin NS, Ozdolap S, Sarikaya S, Keskin SI. Bone mineral density and bone turnover markers in patients receiving a single course of isotretinoin for nodulocystic acne. *Int J Dermatol*. 2008;47(6):622-625. doi:10.1111/j.1365-4632.2008.03534.x
34. Spring LK, Krakowski AC, Alam M, et al. Isotretinoin and Timing of Procedural Interventions: A Systematic Review With Consensus Recommendations. *JAMA Dermatol*. 2017;153(8):802-809. doi:10.1001/jamadermatol.2017.2077
35. Waldman A, Bolotin D, Arndt KA, et al. ASDS Guidelines Task Force: Consensus Recommendations Regarding the Safety of Lasers, Dermabrasion, Chemical Peels, Energy Devices, and Skin Surgery During and After Isotretinoin Use. *Dermatol Surg*. 2017;43(10):1249-1262. doi:10.1097/DSS.0000000000001166
36. Huang YC, Cheng YC. Isotretinoin treatment for acne and risk of depression: A systematic review and meta-analysis [published correction appears in J Am Acad Dermatol. 2018 Feb;78(2):431. doi: 10.1016/j.jaad.2017.10.041]. *J Am Acad Dermatol*. 2017;76(6):1068-1076.e9. doi:10.1016/j.jaad.2016.12.028
37. Lee SY, Jamal MM, Nguyen ET, Bechtold ML, Nguyen DL. Does exposure to isotretinoin increase the risk for the development of inflammatory bowel disease? A meta-analysis. *Eur J Gastroenterol Hepatol*. 2016;28(2):210-216. doi:10.1097/MEG.0000000000000496
38. Nagler AR, Milam EC, Orlow SJ. The use of oral antibiotics before isotretinoin therapy in patients with acne. *J Am Acad Dermatol*. 2016;74(2):273-279. doi:10.1016/j.jaad.2015.09.046
39. Rashtak S, Khaleghi S, Pittelkow MR, Larson JJ, Lahr BD, Murray JA. Isotretinoin exposure and risk of inflammatory bowel disease. *JAMA Dermatol*. 2014;150(12):1322-1326. doi:10.1001/jamadermatol.2014.1540

40. Öztürk S, Öztürk T, Ucak H, et al. Evaluation of ovarian reserve and function in female patients treated with oral isotretinoin for severe acne: an exploratory study. *Cutan Ocul Toxicol*. 2015;34(1):21-24. doi:10.3109/15569527.2014.888079
41. Ganceviciene R, Zouboulis CC. Isotretinoin: state of the art treatment for acne vulgaris. *J Dtsch Dermatol Ges*. 2010;8 Suppl 1:S47-S59. doi:10.1111/j.1610-0387.2009.07238.x