

Indication, Contraindication, Complication and Monitoring of Isotretinoin

Abstract

Acne is the most prevalent skin disorder affecting primarily adolescents and young adults. Side effects of acne, such as scarring, dyspigmentation, and low self-esteem, can cause severe morbidity. Isotretinoin is a medication that is used to treat severe acne. The medicine was licensed by the Food and Drug Administration in 1982 to treat severe nodular acne that had been resistant to other treatments, including systemic antibiotics. Other indications of isotretinoin include moderate acne, cutaneous T-cell lymphomas, neuroblastoma, and the prevention of squamous cell carcinoma in high-risk patients. Rosacea, folliculitis, and pyoderma faciale have all been treated with isotretinoin. Some side effects are also associated with the use of isotretinoin including teratogenicity the most severe one. The purpose of this research is to review the available information about indication, contraindication, complication and monitoring of Isotretinoin. Various dermatological conditions are also treated with isotretinoin apart from the common indication of acne. Complete blood count along with the lipid profile, and liver function test are monitored in patients on isotretinoin therapy. Dry lips and dry skin are among the common side effects of isotretinoin. Due to the severe complication of teratogenicity isotretinoin is contraindicated among pregnant women. Evidence from the literature suggests that isotretinoin is the effective medication in treatment of acne and low dose of isotretinoin does not cause any complication. Evidence-based guidelines and strategies for safety and efficacy of isotretinoin can be developed by further clinical research and trials.

Keywords: *acne, isotretinoin, indication, complication*

Introduction:

Acne is a persistent, inflammatory, and immune-mediated condition of pilosebaceous domain that is quite common in teenagers. It affects the face, trunk, and back; it can leave scars and have a negative impact on one's quality of life. The key to disease resolution is early, effective, and safe therapy. Oral isotretinoin is the only treatment for moderate and severe acne that cures or prolongs remission while also reducing psychosocial effects and scarring. It

has anti-inflammatory and immunoregulatory effects, as well as inhibiting sebaceous gland activity. No other therapeutic approach, including topicals paired with oral antibiotics, achieves the same results. Recurrence following non-isotretinoin therapies is common, increasing the risk of scarring, impairing skin attractiveness, and creating emotional anguish in youth. Isotretinoin should be the first line treatment for moderate to severe inflammatory acne if there are no absolute contraindications (1). Acne is the most prevalent reason for consulting a dermatologist, as per the epidemiological surveys conducted around the world. Acne is the second leading cause of disability among skin ailments, second only to dermatitis, according to a 2013 global burden of disease research. Between the ages of 16 and 20, the prevalence of acne surges. Acne affects more than 80% of teenagers in population-based epidemiological studies that focus on them. Acne has been shown to have negative impacts on quality of life that are comparable to those produced by other chronic conditions such as diabetes, asthma, and arthritis (2).

In 1982, the Food and Drug Administration approved oral isotretinoin as a therapeutic solution for severe acne. Isotretinoin's efficacy has not been surpassed by any other medication, and it remains the most clinically effective anti-acne therapy, delivering long-term remission and significant improvement in many patients, more than two decades later. Isotretinoin is the only acne treatment that affects all of the primary etiological causes. It accomplishes this amazing potency by interfering with cell division, differentiation, survival, and death. It reduces sebum production significantly, impacts comedogenics, reduces surface and ductal *Propionibacterium acnes* and has anti-inflammatory actions. Within 6 weeks, a dosage of 0.5–1.0 mg/kg/day drastically lowers sebum secretion by the order of 90% (3). Despite the introduction of several treatments, oral isotretinoin is the most effective and impacts all elements involved in the disease's etiology. In the treatment of properly selected acne patients, oral isotretinoin appears to provide the best results and the fewest side effects (4).

The usage of isotretinoin should be carefully examined because some of the side effects might be fatal. Isotretinoin use has been linked to serious side effects, including teratogenic complications. The mucocutaneous effects on the lips, eyes, mouth, and other epidermal surfaces are the most common side effects. Liver function tests, cholesterol levels, and other blood indicators must all be monitored. Also, due to the isotretinoin's teratogenic risk, it must be used in conjunction with a contraceptive program that includes the use of effective contraceptive methods as well as pregnancy monitoring before, during, and after treatment

(5). The purpose of this research is to review the available information about indication, contraindication, complication and monitoring of Isotretinoin.

Methodology:

This study is based on a comprehensive literature search conducted on June 16, 2022, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about indication, contraindication, complication and monitoring of Isotretinoin. There were no restrictions on date, language, participant age, or type of publication.

Discussion:

Isotretinoin is the only acne treatment that targets all of the key causes of acne. Unlike antibiotics, oral isotretinoin has no direct effect on microbial cells. It significantly lowers the rate of sebum secretion and the size of the sebaceous glands. Because the medication reduces sebum secretion, it also reduces follicular hyperkeratinisation and changes the milieu within the duct, resulting in better *Propionibacterium acnes* suppression than topical or oral antibiotics. Acne inflammation is reduced due to the substantial reduction in the *Propionibacterium acnes* population. In acne, oral isotretinoin reduces inflammatory activity at the cellular level and normalizes overactive toll-like receptor-mediated innate immune responses (2). Acne is a chronic inflammatory relapsing condition that primarily affects adolescents, with scarring as a common complication. Early and adequate treatment allows for better disease management, extended remission, scar reduction, and improved quality of life. Systemic isotretinoin can be utilized in severe acne as well as moderate acne that is resistant to conventional systemic treatments, according to the therapeutic algorithm. Acne severity and quality of life improve after treatment with systemic isotretinoin (6).

Indication for Isotretinoin

While isotretinoin has transformed the treatment of acne vulgaris, it is now becoming more widely recognized as a viable therapeutic choice for a variety of other cutaneous disorders. Isotretinoin is used for a range of dermatological conditions, including hidradenitis suppurativa, sebaceous gland pathology, rosacea, scarring alopecia, cosmetic dermatology,

and non-melanoma skin cancer prevention. Isotretinoin is a well-tolerated medicine with promise as an adjuvant treatment or a second-line agent in people with disease refractory to first-line therapy when administered in the right cohort and with appropriate prior counselling about adverse effects. Although there has been interest in using isotretinoin for purposes other than acne treatment, the majority of studies presented are case studies or limited retrospective reviews (7). Fulminant rosacea is a distinct, unusual, and extremely inflammatory form of rosacea that manifests as papules, pustules, nodules, and sinus tracts draining a sero-purulent, coalescent secretion in the centre of the face. Isotretinoin along with prednisone, 40–60 mg/day, is the preferred treatment. It is recommended to start with a daily dose of 0.2–0.5 mg/kg and gradually increase to 0.5–1 mg/kg over three to four months (8).

Findings of a systematic review in 2021 revealed that other than acne treatment isotretinoin is also used for Rosacea (0.22-1 mg/kg/day), cutaneous T-cell lymphomas (0.5-2 mg/kg/day), and non-melanoma skin cancers (0.2-8.2 mg/kg/day). Inflammatory conditions like rosacea, granuloma annulare, and hidradenitis suppurativa benefit from lower oral isotretinoin doses of 0.3-1 mg/kg/day, whereas hyperkeratotic diseases like psoriasis and pityriasis rubra pilaris respond better to higher doses of up to 2-4 mg/kg/day for lesion clearance. For rosacea, psoriasis, granuloma annulare, Darier's disease, dissecting cellulitis, and non-melanoma skin malignancies, recurrence of disease after withdrawal of isotretinoin has been observed. Exacerbation of hidradenitis suppurativa has been found in some cases. Isotretinoin off-label is an excellent therapy option for dermatological disorders other than acne. For maximal efficacy and safety, further prospective, randomized human trials are needed to determine when and how to use off-label isotretinoin (9).

Bazargan stated in his systematic review study that the most effective treatment for moderate to severe acne is oral isotretinoin, which has largely dose-dependent side effects. Low dose isotretinoin which is 0.5 mg/kg/day for 1 week every 4 weeks for 6 months could be effective and even comparable to high or optimal doses in the end result (10). Isotretinoin, like tretinoin and acitretin, works to regulate psoriasis by converting keratinocytes in the cytoplasm into all-trans retinoic acid, which enters the nucleus, binds to nuclear receptors, and activates particular areas of DNA involved in cell proliferation, differentiation, and apoptosis. As a result, it lowers keratinocyte hyperproliferation, which is one of the events implicated in the pathogenesis of psoriasis (11). Moderate acne, cutaneous T-cell lymphomas, neuroblastoma, and the prevention of squamous cell carcinoma in high-risk patients have all

been treated with isotretinoin. Isotretinoin has also been used to treat rosacea, folliculitis, and pyoderma faciale by dermatologists (12).

Complication and Contraindication of Isotretinoin

Although effective in the treatment of severe acne however, isotretinoin is a potent human teratogen. Congenital abnormalities, such as craniofacial, cardiovascular, neurological, and thymic anomalies, are believed to be 20%–35% common in infants exposed to the drug in utero. Even in the absence of physical deformities, 30–60% of children exposed to isotretinoin prenatally have been documented to have neurocognitive impairment (13). Vallerand concluded in his study that oral isotretinoin can minimize acne lesion numbers more effectively than other acne treatments. However, when compared to the control group, adverse effects are more common with oral isotretinoin, and they may be more probable to occur at higher daily dosages. The majority of isotretinoin side effects are minor dryness-related skin symptoms, with Stevens-Johnson Syndrome, severe cheilitis, severe xerosis, severe acne flare, photosensitivity, elevated liver enzymes, decreased appetite, headache, and depressed mood affecting only 3.2% of patients randomized to isotretinoin (14).

Findings from a retrospective review revealed that the most common side effect was dry lips, which affected 100% of users, preceded by xerosis among 94.97% of participants, and facial erythema in 66.21% of patients. Psychiatric symptoms accounted for 25.16% of all side events, while eye abnormalities accounted for 8.96%. A rise in total cholesterol and serum triglycerides was discovered during laboratory tests. The side effects were moderate and well-tolerated, and the treatment did not have to be stopped. However, it is critical to inform patients about this severe complication (15). Results of a cross-sectional study in 2020 showed that arthralgia was seen in 47.9% of the patients, myalgia in 53.2%, low back pain in 70.2%, sacroiliitis in 11.7%, and tendonopathy in 4.3% of patients using isotretinoin. Inflammatory pain was found in 37.8% of the 66 individuals with low back pain, while mechanical pain was seen in 62.2%. In 11 individuals with inflammatory back pain, sacroiliac magnetic resonance imaging revealed bone marrow edema consistent with sacroiliitis. Individuals with low back pain received a considerably greater total cumulative dosage of isotretinoin than patients without low back pain ($p = 0.014$) (16).

Hanna stated that isotretinoin therapy should be approached with caution by psychiatrists since it has the potential to provoke episodes of affective disorders, especially in patients with a family history of affective disorders or previous episodes of mental illness. Isotretinoin

medication for acne patients with a family history of affective disorders or prior experiences of mental illnesses necessitates extra caution and care, and if signs of depression arise or intensify during treatment, a dermatologist and a psychiatrist must collaborate (17). Isotretinoin's specific molecular mechanism of action is unknown; nonetheless, oral isotretinoin acts on all key processes of acne pathogenesis at the same time. Various reports regarding the risk of teratogenicity and depression from isotretinoin use, as well as the implementation of intensive prevention programs, have established a barrier to the use of isotretinoin, the most aggressive acne treatment available, portraying it as an extremely risky regimen (18).

Patients who are pregnant or who are likely to become pregnant are absolute contraindications for the administration of isotretinoin. While, other relative contraindications include isotretinoin or component hypersensitivity, Hypervitaminosis A, leukopenia, hyperlipidaemia, and significant hepatic dysfunction. Breastfeeding mothers, have dose dependent interactions of isotretinoin therapy. The established interactions of isotretinoin include tetracycline group of antibiotics, Vitamin A or vitamin A derivatives, micro dosed progesterone preparations while several case reports of interaction with alcohol and antiepileptics are also present (19).

Monitoring of isotretinoin

American Academy of Dermatology recommends lipid and liver profile monitoring at baseline at least once throughout therapy however, most clinicians continue to monitor laboratory measures like lipid and liver profiles and complete blood counts on a monthly basis (20). Results of a cohort study in 2021 showed that triglyceride and liver function testing abnormalities of grade 3 or above were found in fewer than 1% and 0.5% of 1,863 patients treated with isotretinoin, respectively. There were no grade 3 or higher cholesterol or complete blood count abnormalities found. The frequency of laboratory monitoring did not alter significantly over time. Despite the fact that laboratory abnormalities are uncommon and rarely have an impact on care, frequent laboratory monitoring is nonetheless a standard practice (21). Results of retrospective study in 2021 concluded that changes in serum transaminase and lipid profiles are unlikely to occur when isotretinoin is used. However, physicians should be cautious when prescribing isotretinoin to individuals who have a history of aberrant results (22).

Results from national survey of dermatologist showed that more than 60% of respondents had a complete blood count, liver function test, and lipid panel done. A monthly lipid panel and liver function test are checked by 74% of dermatologists surveyed, while a monthly complete blood count is checked by 57%. 75% of participants stated that they stopped isotretinoin therapy when patients' alanine transferase and aspartate transferase levels reach 3 times normal, while 89% respondents stopped therapy when patients' levels were 4 times normal. When triglycerides reach four times their normal level, 72% of physicians discontinued the use of isotretinoin. Although the majority of dermatologists questioned monitoring a lipid panel and liver function test, there is no unanimity on isotretinoin monitoring tests and frequency (23). Findings of retrospective study in 2019 concluded that minor clinical and reversible complete blood count abnormalities, mild to moderate elevations of liver transaminases, and serum lipids were the most common laboratory abnormalities in patients on isotretinoin therapy. Because these abnormalities are reversible even if isotretinoin therapy is continued, there is often no need to stop treatment due to test abnormalities, and frequent biochemical monitoring is not advised (24). Well-established literature is present regarding isotretinoin use safety, complications and monitoring however, more clinical research and randomized clinical trials can be significant contributor to literature and also aid in designing more safe and effective guidelines for isotretinoin therapy.

Conclusion:

Isotretinoin is an effective treatment for acne that ranges from moderate to severe. Low-dose isotretinoin is a successful modality of treatment with a low incidence of severe side effects and at a lower cost because the benefits to society exceed the hazards. Future research can be helpful in establishment of safe and effective guidelines for the use of isotretinoin therapy with the clinical evidence.

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