

Physiological and Psychological Effects of Isotretinoin in the Treatment of Patients with Acne: A Narrative Review

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Abstract: Isotretinoin (ISO) is a powerful vitamin A derivative that offers the potential for treatment of permanent remission of acne; however, its potential side effects on both physiological and psychological aspects limit its application. This article reviews the side effects of ISO from physiological and psychological aspects in detail, to better screen the suitable population of ISO and improve the efficiency of clinical treatment. Our findings indicate that ISO may cause teratogenicity, skin reactions, ocular reactions, changes in blood indicators, and occasional acne fulminans. To optimize clinical treatment, more attention should be paid to identifying the specific conditions under which these reactions occur, how severe they are, and how they subside to alleviate patient concerns. Regarding the controversial issue of psychological side effects caused by ISO, researchers should shift their focus to the psychological problems that acne itself may cause.

Keywords: acne, isotretinoin, physiological effects, psychological effects

Introduction

Acne vulgaris (AV) is a chronic, immune-mediated, multifactorial inflammatory disease affecting the hair sebaceous gland units,¹⁻³ which is one of the most common skin disorder afflicting adolescents worldwide.^{4,5} Isotretinoin (ISO) is a powerful vitamin A derivative, and it is the only possible treatment for permanent remission of acne. Its action mechanism is to normalize the differentiation of follicular keratinocytes by reducing the size and secretion of sebaceous glands, inhibiting the growth and inflammatory response of keratinocytes in acne.⁶ ISO is the only therapy that affects all major causes of acne.^{7,8} Since oral ISO was first approved by the US Food and Drug Administration (FDA) in 1982 for the treatment of severe acne,⁷ oral ISO has been proven to be a major pharmacological breakthrough in the treatment of severe and recalcitrant cases with acne.⁹ However, ISO has three prominent adverse reactions: (1) psychological problems, (2) inflammatory bowel disease (IBD), and (3) teratogenicity.¹⁰ Yilmaz et al¹¹ reported that genotoxicity, teratogenicity, and carcinogenicity information of ISO was very limited and controversial. Nevertheless, the claims about side effects of ISO had led many patients to hesitate to use it.

The psychological side effects of ISO treatment for acne on patients are still vague, and the types of skin reactions and blood changes associated with the treatment are occasionally debated. Ko et al¹² found that the medical personnel group evaluated ISO as more neutral, while the non-medical personnel group rated ISO as more negative, based on YouTube. Due to the mysteries of ISO, this article reviews the side effects of ISO from both psychological and physiological aspects to better screen the suitable population.

Methods

A review of the literature was conducted using PubMed, with the search formula “(Acne [Title/Abstract]) AND ((Isotretinoin[Title/Abstract]) or (ISO[Title/Abstract]))” and the time limit was after 2018.

Four hundred and seventy-four articles were initially included, and after screening the titles, abstracts, and relevant references, there were 160 articles left. Then we removed the duplicate expression, 127 articles were ultimately included in this research.

Results

Physical Effects

The incidence of adverse reactions after 3 months in patients with ISO was 40% in a Nepal study.¹³ Vallerand et al¹⁴ collected data from 11 trials meeting eligibility for review (total 760 patients randomized) and found that the rate of adverse events was twice as high in the ISO group compared to the control group across all trials. In a 2022 study by Brzezinski et al¹⁵ of 90 adolescent participants treated with ISO for acne, 11 different adverse effects were noted during ISO treatment. Next, we begin to tease out the physical side effects of ISO treatment with the three prominent adverse effects mentioned above.

IBD

ISO has sparked many discussions about its potential association with IBD. Reddy et al¹⁶ reviewed all of the adverse reports filed with the FDA from 1997 to 2002, and eighty-five cases of IBD associated with ISO use were reported. Das et al¹⁷ showed that ISO caused development of IBD related macroscopical and histopathological alterations, scholars experimented with mice and found that the frequency of defecation in animals after ISO treatment increased over time, eventually leading to bloody stools.

A retrospective cohort analysis that Wright et al¹⁸ did showed that 6-month IBD incidence among AV patients with ISO treatment was very low, even similar to AV patients without ISO (0.08% vs 0.04%). Many scholars found no evidence supporting that ISO caused IBD/ulcerative colitis.^{14,19} Sakhamuru et al²⁰ reviewed 33 publications and found that most studies showed no significant association between the use of ISO and the development of ulcerative colitis. The Brazilian Society of Dermatology appointed eight experts from five universities to reach a consensus on the indications for ISO, and the experts agreed that there was no causal relationship between IBD and ISO.¹

Although the incidence of IBD in patients treated with ISO is low, the consequences for an individual developing IBD may be significant.²¹ Doctors can avoid providing ISO to IBD susceptible patients as much as possible by inquiring about family or personal medical history, in order to avoid serious consequences.

Pregnancy and Teratogenicity

ISO has adverse effects on the pituitary-ovarian axis, which can enhance granulosa cell apoptosis and reduce follicular reserve.²² In the study conducted by Schaefer et al,²³ ISO was considered the most teratogenic drug after thalidomide. Even a simple capsule may cause congenital malformations within the first trimester.²⁴

ISO played a role in teratogenicity.²⁵ Natural abortion, dysgnosia, craniofacial defects, central nervous system, and endocrine system disorders, are all potential birth defects.²⁶ The mean age of ISO users is approximately 24 years old,²⁷ which means that users are mostly women of childbearing age. According to data reported by Sladden et al,²⁸ in pregnancies which the fetus was exposed to ISO, the risk of spontaneous abortion and embryopathy was approximately 20% and 18% to 28%, the main abnormalities were craniofacial, thymic, cardiac, and central nervous system. Of the 19 pregnancies in which the fetuses reached a viable gestational age in the retrospective case series reported by Lammer et al,²⁹ 2 resulted in malformed stillborn infants and 14 in malformed liveborn infants. Of the 36 prospectively identified ISO-exposed pregnancies reported by Lammer et al,²⁹ 8 resulted in first-trimester spontaneous abortion, 1 in a malformed stillborn infant, and 4 in live-born infants with at least one major malformation. A report contained 151 births exposed to ISO reported by Dai et al,²⁴ 47% had congenital malformations. Of 94 prospectively ascertained pregnancies that ended in births, 28% had congenital malformations.²⁴

Due to the teratogenic effect of ISO, both Europe and the United States had strict requirements for the prevention of pregnancy in female patients to prevent fetal abnormalities caused by ISO.^{26,30,31} This means that the ISO is strictly restricted for women users and these users are required to use contraception during the time.

Acne Fulminans (AF)

AF is a severe form of inflammatory acne.^{32–34} It might begin during ISO treatment and also may occur spontaneously,^{35,36} primarily affecting adolescent males with pre-existing AV.^{35–37} In some patients, mild cystic acne with ISO rapidly progressed to ulcerative and necrotizing acne with systemic symptoms.^{33,35}

Sánchez-Velázquez et al³² reported an acne adolescent with a history of overweight started with ISO at a dose of 0.4 mg/kg/day had worsened acne after six-week treatment with pustules, numerous painful papules, and hemorrhagic nodules crusting on the back and chest. He was diagnosed with ISO-induced AF, then he was advised to stop taking ISO and prednisone 1 mg/kg/day was initiated. ISO was reintroduced at 0.1 mg/kg/day after four weeks, however, when the patient attempted to reduce prednisone or increase ISO, he experienced multiple truncal flare ups. Finally, the adolescent achieved complete remission after being treated with apremilast monotherapy.

The possible biological mechanisms for ISO-induced AF are as follows: Short-term exposure to ISO in sebum cells increases the intracellular lipid content and the expression of sterol regulatory element-binding protein (SREBP)-1 and arachidonic synthetase 5-lipoxygenase (LOX).⁸ The upregulation of SREBP-1 and 5-LOX may lead to AF because of their participation in sebum production.³⁸

The reasonable treatment for ISO-induced AF with systemic symptoms is oral corticosteroids at a dose of 0.5–1 mg/kg/day for more than 4 weeks until AF subsides.³² Researchers reported that ISO in combination with systemic steroids or other anti-inflammatory agents, adalimumab, and 5-Aminolevulinic acid photodynamic therapy (ALA-PDT) might be effective means in treating AF.^{35,39,40} In terms of dose, Zaba et al³⁵ once suggested a pathogenic dose: 0.5–1 mg/kg/day, and the duration of treatment before the origin of AF was an average of 3 weeks (range, 1 to 7 weeks). Borghi et al⁴¹ found that for ISO treatment of acne, the number of AF cases starting at a dose ≤ 0.2 mg/kg/day was smaller than the number of AF cases starting at a dose of 0.5 mg/kg/day ($P < 0.05$) during the first 4 weeks of treatment, and the efficacy was not different from therapies starting with higher doses (0.5 mg/kg/day). It had also been suggested that the presence of multiple large pimples in the first few weeks of taking ISO appeared to be a momentous risk factor for acne outbreaks.⁷

Skin Reaction

During ISO treatment of acne, more than half of the adverse events were skin diseases and related to dryness, dry skin was the most common adverse reaction, and desquamation of the skin and mucous membranes were common side effects.^{13,14,30} It might be because that treatment with ISO could result in a decrease in skin hydration.⁴² In the study proved by Brzezinski et al,¹⁵ concluding 90 teenagers with acne treated with ISO, the incidence of dry lips was 100%. Chapped lips were also the adverse reaction.^{38,43} However, evening primrose oil as a dietary supplement was considered safe, which could result in a significant increase in skin hydration in patients treated with ISO, and significantly ameliorate the adverse effects such as dryness, lip cracking, and peeling skin.⁴² Retinoid dermatitis, burning sensation, and itching sensation were all adverse reactions caused by ISO, among the side effects of mucocutaneous, cheilitis was the most common adverse effect and dose-dependent.^{38,43} Zainab et al⁴⁴ demonstrated that omega 3 could be used to prevent or manage cheilitis, xerosis or dry lips. The ISO side effects of various mucocutaneous and central nervous systems were mostly dose-related.⁴⁵ For the skin side effects of ISO, they were usually reversible, dose-dependent, predictable, and manageable.^{30,46} The absence of these reactions raised the possibility of underdosing.⁴⁷

ISO is a retinol derivative of vitamin A and has an impact on the formation of collagen.⁴⁸ In addition, ISO inhibited collagenase and gelatinase activities in stimulated fibroblasts in vitro, which affect collagen formation.³⁵ What is more, Retinoids are known for increasing skin vulnerability by reducing the number of tensin filaments and desmosomes attached and the secondary accumulation of amorphous material in the epidermis.³⁵ These may partly explain the keloid in some patients.

Ocular Reaction

ISO was also associated with ocular changes, mainly in the ocular surface. Acar et al⁴⁹ found that systemic ISO treatment effected both ocular surface parameters and corneal and meibomian glands structure in a prospective study. Dry eye disease, eyelid conjunctivitis, abnormal or atrophy of meibomian gland secretion, chalazion or styne were common

adverse reactions. Other events such as corneal opacity, photophobia, refractive changes, keratitis, impaired night vision/color vision, and papilledema were rare.⁵⁰ In addition, ISO treatment has been associated with neuro-ophthalmic abnormalities, dark adaptation and worsening color vision, cataracts, and retinal toxicity such as premacular bleeding, serous retinal detachment, vascular occlusion, and vitreous abnormalities.^{30,51–53} What's more, the use of ISO could result in an increase in the area of retinal pigment epithelium-Bruch membrane complex and ellipsoid zone with short term.⁵⁴

In the study by Shrestha et al,¹³ dry eyes were one of the adverse effects after 3 months of oral ISO treatment. Nearly all dermatologists prescribed lubricant eye drops routinely for patients in ISO treatment in Egypt.⁵⁵ Villani et al³⁰ also found that patients might experience dry mucous membranes, such as eyes, nose, and mouth, when the dose was too high for them. This might be because systemic ISO administration altered the function and structure of meibomian glands and inhibited lipid production, resulting in rapid tear evaporation.^{56,57} ISO also could cause tear film instability with Meibomian gland dysfunction and change of morphology and may cause evaporative type of dryness.⁵⁸ In addition, it altered the conjunctival epithelium, affected the morphology of goblet cells, and interfered with mucin production.^{56,59} What is more, the level of the tear was associated with the use of ISO and an increase in bacterial flora in the conjunctiva.⁵⁶ After the use of artificial tears consisting of 0.2% galacto-xyloglucan and 0.4% hyaluronic acid, both symptoms and tear rupture time were improved in subjects treated with oral ISO.⁵⁶

Compared with healthy group, acne group had higher scores on the total eyelid and meibomian gland secretion.⁶⁰ Compared with the control group, the meibomian glands, the thickening, thinning, tortuosity, and presence of ghost areas were statistically significantly more common in the AV group on the morphological evaluation.⁶⁰ This means that when exploring the side effects of ISO treatment in acne patients on the eye, the effect of acne itself needs to be excluded.

Other Reactions

Shrestha et al¹³ found that adverse effects after 3 months of oral ISO treatment also included hair loss. Hair loss was a less common side effect.⁶¹ Age, cumulative dose and duration of treatment were the factors affecting hair loss.⁶¹ Patients who received ISO ≥ 0.5 mg/kg/day were more likely to have hair loss than those who received ISO < 0.5 mg/kg/day (5.7% vs 3.2%).⁶² Researchers reported that menstrual irregularity and hirsutism could be observed,^{63,64} and ISO gradually increased the nail growth rate and thinned the nail plate over time.⁶⁵ Researchers found that ISO caused musculoskeletal side effects,⁶⁶ such as arthralgia, myalgia, back pain, and symptoms associated with spondyloarthropathy and sacroiliac arthritis,³⁰ but did not alter muscle strength.⁶⁷ Webster et al⁶⁸ reported that nearly half of patients on ISO develop elevated levels of creatine kinase, a proxy for potential muscle tissue damage. Pain severity is directly correlated with the cumulative dose of ISO and the increasing age.⁶⁹

Hareedy et al⁷⁰ considered the effects of ISO on liver, kidney, and hematological function, potential oxidative stress associated with ISO treatment: ISO treatment might be associated with oxidative stress, liver and lipid abnormalities in acne patients. Hepatic dysfunction occurred in up to 15% of patients taking ISO.⁷¹ Serum ferritin increased while serum ceruloplasmin decreased. ISO was associated with a possible positive nitrogen balance (increased protein) and elevated blood urea nitrogen and uric acid levels.

Zane et al⁷² found that ISO use could cause leukopenia, neutropenia, agranulocytosis, thrombocytopenia, thrombocytosis, and other abnormalities in hematological parameters. Cosansu et al⁷³ found that low-density lipoprotein cholesterol, serum total cholesterol, aspartate aminotransferase levels, and triglyceride increased after ISO treatment. When the treatment in advance hemogram parameters of the patients and the values in the third month were compared, no statistically significant differences were detected in the lymphocyte count, monocyte count, platelet-to-lymphocyte ratio, and monocyte-lymphocyte ratio.⁷³ Inflammatory and non-inflammatory lesions were significantly reduced after 3 months of oral ISO at a dose of 0.5–0.7 mg/kg/day.¹³ Besides, when other parameters were evaluated, total white blood cell counts, neutrophils, lymphocytes, monocytes, basophils, and platelets did not change from baseline, however, there was a significant decrease in mean GAGS score, total, inflammatory and non-inflammatory lesion counts, eosinophils, and absolute eosinophil count.¹³ Hareedy et al⁷⁰ shared that ISO could affect immune regulation (lowering the ratio of neutrophils to lymphocytes) and was associated with blood abnormalities. What is more, ISO might have a sensitization effect.⁷⁴

Researchers have found that ISO treatment causes significant changes in hormone levels, thyroid gland hormones decrease and pituitary thyroid-stimulating hormone levels increase, and the observed changes in hormonal levels were increased with the augment of therapy.⁷⁵

Some scholars, such as Toossi et al⁷⁶, proposed that ISO caused low serum vitamin D levels and that there was a correlation between acne and serum vitamin D deficiency. Shrestha et al¹³ put forward the opposite view, they concluded that patients with moderate to severe acne had low vitamin D levels, that no change in vitamin D levels was found after short-term treatment with oral ISO, and that there was no significant association between acne and serum vitamin D deficiency.

Psychological Effects

For a long time, many researchers harbored the idea that ISO involvement in treatment could result in psychological reactions, such as low mood, depression, anxiety, and suicide. ISO is a derivative of vitamin A and has many adverse side effects similar to those patients with high doses of vitamin A. The adult brain is sensitive to exposure to excess retinoic acid (the metabolite of the vitamin). Retinoic acid may be linked to psychological problems by observing the overlap of brain regions implicated in retinoic acid function, stress, and depression.⁷⁷ What is more, treatment with 13-cis-RA increased 5-HT1A protein and serotonin reuptake transporter protein levels, it might result in the decrease of serotonin availability at synapses.⁷⁸ Chaos in serotonin levels is closely related to depression and emotional problems.^{77,79} In addition, Bremner et al⁸⁰ found that the use of ISO was associated with decreased brain metabolism in the orbitofrontal cortex, which meant the onset of mediate depression.

Studies in both animals and human show that ISO can lead to depressive behaviors.^{77,78} On the contrary, some scholars found that the use of ISO was not associated with the increased risk of depression in acne patients.^{81–84} Some scholars reported that patients with ISO experienced a lower risk of depression compared to those with oral antibiotics.^{85–87} What's more, acne treatment appeared to improve depressive symptoms.⁸²

In a retrospective cohort research conducted by Sundström et al⁸⁸ in Sweden, the risk of attempted suicide increased significantly six months after the ISO treatment, but the risk due to ISO cannot be calculated solely, because the risk has already been rising before treatment. Female gender, assessment by Consultation-Liaison Psychiatry, and absence of protective factors were linked to increased suicidality risk.⁸⁹ Psychiatric history and anxiety history were risk factors for suicide attempts in ISO users.^{90,91} On the contrary, the researchers found that acne patients with suicidal ideation or attempts in the general population were 1.47 times than those taking ISO, patients taking ISO might have a lower rate (8.4/100 000 vs 11.8/100 000 in 2009; 5.6/100 000 vs 12.1/100 000 in 2010) of complete suicide than the general US population.^{92,93} ISO treatment for acne may reduce suicidal behavior.⁸⁸ What is more, Sundström et al⁸⁸ indicated that if acne could not be effectively resolved, the risk of suicide would increase because of the severity of the psychological burden of acne by a retrospective cohort study.

The scholars found that psychiatric or psychosomatic symptoms were common in ISO treatment.¹⁴ Bray et al⁹⁴ investigated whether ISO treatment resulted in changes in the concentration of key mood-related neurotransmitters, but the amount of patients who agreed to follow-up was too small to draw a conclusion, leading to speculation that it was related to mood factors. By contrast, experts in Brazil and Spain agreed that there was no evidence of a causal relationship between ISO on psychological effects.^{1,90} Chen et al⁹⁵ reported that there was no increased risk of psychiatric disorders in acne patients with ISO, whatever dosage and duration of treatment were. Tapio et al⁸⁶ also obtained similar results by observing changes in mental status following ISO use in more than 30,000 cases, ISO was not independently related to exorbitant mental adverse outcomes, and the relation between increased acne severity and incidence of adverse mental results was reported. What is more, Tapio et al⁸⁶ also reported that compared with acne patients who were propensity score-matched and prescribed oral antibiotics, ISO was associated with lower rates of anxiety, sleep problems, non-fatal self-harm, and prescription of psychotropic medications. Similarly, Kridin et al⁸⁵ also reported that patients under ISO had less psychological distress,⁸⁷ lower risk of post-traumatic stress disorder, anxiety, bipolar disorder, schizophrenia, and adjustment disorder relative to those treated with oral antibiotics.

Dose Related Effects

Different doses of ISO may influence whether side effects occur. American Academy of Dermatology Guidelines (2016) gave a reference dose: ISO treatment should start at a dose of 0.5 mg/kg/day, increase to 1 mg/kg/day, and continue until a dose of 120–150 mg/kg (severe acne) is reached.³⁰ For patients with moderate acne, the recommended dose is 0.3–0.5 mg/kg/day. Previous studies have shown nearly the same results: to enhance response rates and prevent a recurrence, the recommended dose was 0.5–1.0 mg/kg/day for 12–16 weeks, with a recommended cumulative dose of 120 mg/kg.^{96,97} European guidelines also offered dose recommendations in 2016 based on the severity and type of acne: 0.3–0.5 mg/kg for severe papulopustular and moderate nodular forms of acne and a dose of >0.5 mg/kg for conglobate acne.⁹⁸ Muqarrab et al⁹⁹ showed that conventional-dose (0.5–1.0 mg/kg/d) ISO improves the odds of preventing relapses than low-dose (0.1–0.3 mg/kg/d) in adults with mild-to-moderate AV by a meta-analysis review. Otherwise, it is vital to note that ISO at a dose of 35 mg/kg causes the most severe damage to the intestinal mucosa.¹⁷ The dose is also an issue that cannot be ignored in pregnancy and teratogenicity, low-dose (0.25–0.4 mg/kg/day) ISO in treatment of moderate to severe acne seems to be safer on ovarian reserve.¹⁰⁰

In contrast, an international consensus on acne published by the Global Alliance for Improved Outcomes did not make a specific recommendation for ISO dosage, but it only recommended continuing to use ISO for a month after the acne cleared up, regardless of the cumulative dose.^{101,102} Rademaker¹⁰³ took the attitude that neither daily nor cumulative dosages influenced relapse of AV so long as treatment was continued for ≥ 2 months after the acne had completely resolved. Several scholars also found no difference in recurrence rates between patients taking cumulative doses >120 mg/kg and those taking less than 120 mg/kg.^{102,104–106} ISO cumulative dosage higher than 120 mg/kg had nothing clinical advantage, and may increase the risk of adverse events because of the reduction of compliance.¹⁰⁷

Discussion

Acne vulgaris patients often experience reduced quality of life.¹⁰⁸ Our previous study demonstrated that the more severe the acne severity grading, the greater impact on daily life, social activity and mental health.¹⁰⁹ What is more, the impact of acne on patients varied by gender: females were less tolerant of appearance blemishes, while males were more troubled by physical discomforts caused by acne.¹⁰⁹ However, skin lesions appear most often on the face in the female population.¹¹⁰ This may lead to more serious psychological problems in this group. The above content indicated that acne seriously affects patients' lives. ISO is one of the important drugs for treating acne, the above content of this article reviewed the side effects of ISO from physiological and psychological aspects, to better screen the suitable population of ISO and improve the efficiency of clinical treatment.

For the two opposing views about psychological, we harbored the idea that the reason for the different results might be the psychological problems brought to the patients by the severe acne itself. AV and adolescence are both independent risk elements for suicide and depression.¹¹¹ Therefore, we proposed that subsequent research on the psychological effects of ISO treatment on acne must focus on the serious psychological burden associated with recalcitrant acne. In addition, it is momentous to note that the risk of depression should not be a reason to discourage the use of ISO in patients with moderate to severe acne. Before drug administration, doctors should explain the emotional problems that might be taken by ISO to patients, communicate with the patients more during the treatment, and suspend therapy if clinically momentous depression occurs.¹⁰ In addition, early and effective treatment is vital to reduce the risk of scarring.^{2,112}

Approximately 30% who regularly prescribed ISO in clinicians, had at times chosen not to prescribe ISO to patients with severe acne because of the iPLEDGE program.¹¹³ Due to the abortion bans in some countries, it might cause dermatologists to eschew ISO use in patients of childbearing potential.¹¹⁴ Because of the difficulty of accessing ISO, patients may turn to over-the-counter dietary vitamin A supplements.¹¹⁵ Cook et al¹¹⁶ proved that at doses of 50,000–300,000 IU daily, vitamin A probably supply a second choice for acne management when ISO is unavailable. However, vitamin A was not considered safe enough to be reused because it was easily available and could not be strictly monitored. That means there was a big security risk, the iPledge risk evaluation and mitigation strategy and other programs must actively solve workflow concerns and predict changes that threaten patient access to medication, even in changes.¹¹⁵ Doctors should also do a better job of advising acne patients on medications to avoid tragedies. Vitamin D can act as an immunomodulator, regulating the proliferation and differentiation of keratinocytes and sebum cells, and

has the effect of acne lysis.^{13,117,118} It seems we still need to find out more about the effects of vitamin A and vitamin D on acne. Besides, A single-blind randomized study conducted by de et al¹¹⁹ found that the use of a dietary supplementation containing magnesium, phosphate, minerals and fatty acids in AV for 6 months, 100% of patients experienced complete resolution of symptoms with no reported side effects, and the lesions were more effective than ISO treatment, the pharmacological effect was faster and the long-term curative effect was better after withdrawal. Even seven years after completing treatment, there was no recurrence of AV. Piszczatoski et al¹²⁰ showed that topical clascoterone was likely an effective option for the treatment of AV without systemic side effects by a review. This suggests that there are a lot of potential drugs that academics need to explore.

A systematic treatment escalation based on disease severity, extension, and treatment response are at the core of therapeutic strategies.¹²¹ Since the treatment which could concurrently and safely target all the pathogenic elements implicated in the appearance of acne lesions with minimal side effects did not exist now, we advocated combination therapies.¹²¹ Ma et al¹²² reported that topical antimicrobial peptides combined with low doses (0.3 mg/kg/d) of systemic ISO resulted in considerable improvement of clinical manifestations of mild-to-moderate AV than ISO monotherapy and the reduction in the acne dermatology index turned to be 74.9% with investigator global assessment score 0–1 after 12 weeks. Ye et al¹²³ summarized that oral ISO combined with supramolecular salicylic acid decreased response time compared to ISO monotherapy, with significantly improved global acne grading system (GAGS) score, count of lesions, and efficacy at 4–6 weeks. Skin indices of melanin, pore, erythema, and texture evaluated at week 10 were all enhanced. Oral ISO with or without supramolecular salicylic acid was effective in lesion clearance; only supramolecular salicylic acid significantly enhanced the transepidermal water loss. All the side effects were temporary and tolerable, and no adverse effects were observed. Dixit et al¹²⁴ reported that the combination of oral ISO (0.5 mg/kg/d) with salicylic-mandelic acid (20% salicylic and 10% mandelic acid) was significantly effective than the monotherapy (ISO: 0.5 mg/kg/d) by a comparative double-blind randomized single-center interventional open-label study. And this combination therapy could be used as newer therapy against adult acne without any serious side effects. Salah et al¹²⁵ suggested that oral zinc plus low-dose (0.25mg/kg/d) ISO resulted in the same satisfactory improvement as those who received the standard ISO dosage (0.5mg/kg/d) in moderate to severe AV patients with fewer side effects, and there was no difference regarding the relapse rates between both groups. Ibrahim et al¹²⁶ reported that the combining low-dose ISO (0.25 mg/kg/day) with pulsed dye laser group showed a statistically significantly greater improvement regarding all parameters, such as GAGS, Cardiff acne disability index compared with the standard higher-dose ISO (0.5 mg/kg/day) as monotherapy with less side effects. In a similar way, the ISO and 420 nm intense pulsed light combined treatment played an active role that was clinically significant from AV alleviation perspective in Chinese subjects, lightening basic skin tone and relieving erythema were other major advantages.¹²⁷

Conclusion

In order to better screen the suitable population for ISO and improve clinical treatment efficiency, this article reviewed the side effects of ISO from both physiological and psychological perspectives. Finally, we found that teratogenicity, skin reactions, ocular reactions, changes in blood indicators, and occasional AF caused by ISO were not controversial, which meant that we should pay more attention to how to use medication to reduce these side effects, such as considering combination medication and adjusting drug dosage, in order to provide patients with a better treatment experience. For the most controversial issue of psychological problems caused by ISO, researchers should focus more on the psychological problems caused by acne itself.

Data Sharing Statement

This is a review article. All data generated or analysed during this study are included in this published article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors declare that they have no conflicts of interest in this work.

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