Dean&Francis
ISSN 2959-409X

Molecular Mechanism and Clinical Optimization of Isotretinoin in the Treatment of Acne

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Abstract:

Acne is a very common chronic inflammatory skin disease that can cause permanent scarring and psychological problems. Oral isotretinoin is the first choice for severe and persistent acne. To this day, the exact molecular mechanism of action is not well-known, and thus it has not been applied in clinical practice. With the latest research, this paper will systematically explain the current molecular mechanisms of isotretinoin in the treatment of acne and evaluate its clinical effect and improvement direction. Isotretinoin has some anti-inflammatory and normalising effects on the secretion of the outer layer, changes in cell division of keratinocytes, etc. Based on the above clinical studies, the usual dose of isotretinoin has good clearance in severe acne; a low-dose regimen can also be used to treat mild acne and rosacea. Combination of Laser and Phototherapy Treatment. Generally speaking, the amount of dry skin and mucous membranes after a single dose varies among individuals. Based on current research, it has not been found that isotretinoin causes depression or inflammatory bowel disease. In the future, through nanomedicine formulations, molecular modification and combination therapy, it is expected that isotretinoin will be more effective and safer.

Keywords: Isotretinoin; acne; p53; dosage strategy; combination therapy.

1. Introduction

Acne is a chronic inflammatory skin disease that affects the hair follicle and sebaceous gland, has a very high incidence rate, seriously impacts people's physical and mental health, and can result in permanent scarring [1,2]. The four-fold pathogenetic factors of acne are an excess of sebum production, abnormal keratinisation of the follicular opening, proliferation of Propionibacterium acnes, and inflammation [3,4]. Recently, some studies have shown that at the age of adolescence, a "Westernised diet" rich in carbohydrates and dairy products can increase the levels of insulin-like growth factor 1 (IGF-1) and insulin in

ISSN 2959-409X

the body, thus activating the downstream phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin complex 1 (mTORC1) signaling pathway. This way is the main regulation centre for cell growth and division, as well as metabolism and autophagy; it regulates nutrient sensing and energy balance in the body normally [5]. Activated AKT kinase can inhibit or promote the phosphorylation and nuclear export of some transcription factors, such as forkhead box transcription factor O1 (FoxO1) and FoxO3, and at the same time promote the degradation of p53 protein; it can also reduce the inhibition of androgen receptors (AR), lipid synthesis-related factors and inflammatory signal transducers, thus promoting the occurrence and development of acne [5].

Oral isotretinoin has been one of the top drugs for treating severe acne since its introduction in 1982 [6]. Its first advantage is that it can address the four links of the pathogenic pathway of acne simultaneously [3,7]. Its particular way of action has not been known for a long time. Recently, with the development of transcriptomics research, it has been discovered by scholars that there are certain transcription factor dysregulations in the sebaceous glands of acne patients, and isotretinoin can effectively rectify this condition [5,8]. However, many problems and deficiencies have not been solved in the clinical application of isotretinoin yet. There is a high risk of teratogenicity, and the problems with psychiatric and gastrointestinal diseases have not been solved. In addition, the ideal dosage plan, doctors' concern about prescription, and how to further enhance both the effect and safety of the drug are still unknown in recent years [9, 10].

Based on this, the aim of this article is to explain the molecular basis of acne pathogenesis in detail, thoroughly investigate the contemporary mechanism of action of isotretinoin, and evaluate its current application status and optimisation direction in conjunction with the latest clinical data to provide a reference for personalised treatment. In addition, this review further integrates recent transcriptomic findings with the classical pathogenic mechanisms of acne, providing a more comprehensive explanation of how the IGF-1/PI3K/AKT/mTORC1 pathway and the p53/FoxO1/FoxO3 regulatory network participate in disease progression and isotretinoin response. The article also combines molecular evidence with current clinical strategies, including low-dose regimens, cumulative-dose adjustment, and laser/light-based combination therapy, highlighting the growing importance of personalised treatment in acne management. Furthermore, potential future directions such as nanoparticle delivery systems, selective retinoic acid receptor targeting, and long-term maintenance therapy are discussed to explore ways of improving both the efficacy and safety of isotretinoin in clinical practice.

2. Overview of the Pathogenesis of Acne

The beginning of acne is due to a combination of genes, hormones and the environment. At the bottom, there is an increase in oil secretion, abnormal keratinisation at the opening of the hair follicle and sebaceous gland duct, overgrowth of Propionibacterium acnes, and inflammation. Recently, studies have shown that the aforementioned processes are regulated by an upstream transcriptional regulatory network, and the imbalance of this network is the main molecular reason for the occurrence of acne [5].

Puberty leads to an increase in the amount of growth hormone and sex hormones, and the "Western diet" pattern is high in high-glycemic-load carbohydrates and dairy products; both conditions can significantly increase IGF-1 and insulin in the body, activate the downstream PI3K/AKT signaling pathway, etc. Activated AKT kinase can also phosphorylate many other targets. AKT phosphorylates the transcription factors FoxO1 and FoxO3, moves them from the nucleus to the cytoplasm, and therefore loses the ability to suppress gene transcription in the nucleus. At the same time, AKT phosphorylates MDM2; MDM2 in mice is a negative regulator of the tumour suppressor p53, so it leads to the proteasomal degradation of p53 and reduces its anti-tumour and pro-apoptotic effects [5].

Therefore, there are all sorts of diseases caused by the aforementioned imbalance in transcriptional regulation. A decrease in the level of nuclear FoxO1 removes its suppression of the androgen receptor (AR), SREBP1, PPARγ and signal transducer and activator of transcription 3 (STAT3); thus, there is an increase in sebum production, sebaceous gland cell proliferation and exacerbated inflammation. At the same time, the reduction in FoxO1 also weakens its transcriptional promotion of GATA binding protein 6 (GATA6), which is an important homeostatic regulator in the infundibulum of hair follicles; as a result, there is an overproduction of keratinization at the follicular opening and the formation of microcomedones. The weakening of the inhibitory and pro-apoptotic effects of p53 on the IGF-1 pathway upon degradation will also be more pronounced [5]. In short, the excessive activation of the IGF-1/PI3K/AKT/mTORC1 pathway and the resulting inhibition of p53/FoxO1/3 nuclear activity are the main transcriptional changes in the development of acne.

3. Molecular Mechanism of Isotretinoin in the Treatment of Acne

Isotretinoin is a prodrug; after being absorbed by the cells of sebaceous glands, it is converted into its active form, all-trans-retinoic acid (ATRA), by an internal isomerase. ATRA binds to cellular retinoic acid binding protein 2 (CRABP2), is then transported to the nucleus, and there it binds with the retinoic acid nuclear receptor (RAR) to initiate the expression of certain genes [5].

Recently, research has found that at the molecular level, the main mechanism of action for isotretinoin is to reverse the nuclear inhibitory state of p53, FoxO1 and FoxO3 in the sebaceous glands of acne patients [5, 8].

3.1 Up-regulation of p53 Pathway

ATRA/RAR signaling can directly induce the transcription of the TP53 gene and thereby increase the amount of p53 protein; P53 has several therapeutic effects: it can reduce the expression of IGF-1 and IGF1R to weaken the upstream pro-proliferative signal at the source; it can promote the expression of negative regulators such as phosphatase and tensin homolog (PTEN) and tuberous sclerosis complex 2 (TSC2) to inhibit the PI3K/AKT/mTORC1 signaling pathway; it can increase the expression of the pro-apoptotic protein tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) and pro-autophagic protein autophagy-related 7 (ATG7) to induce apoptosis and autophagy in sebocytes, thus reducing sebum secretion; finally, it downregulates the expression of the anti-apoptotic protein survivin (BIRC5) and androgen receptor (AR) [5].

3.2 Up-regulation of FoxO1/FoxO3 Pathway

p53 can directly induce the transcription of FOXO1A and FOXO3A genes. Rescued FoxO1 in the nucleus can have all kinds of therapeutic effects via multiple paths. FoxO1 is a transcription factor that, with the help of AR, SREBF1, PPARγ and STAT3, decreases the expression of lipids and inflammatory genes. FoxO1 binds to the promoter region of the GATA6 gene, promotes the transcription of GATA6, restores the normal keratinization programme in the infundibulum of hair follicles, and reduces acne. FoxO1 can also suppress the expression of B lymphocyte inducible maturation protein 1 (BLIMP1) to reduce the number of sebaceous gland progenitor cells and further promote sebaceous gland atrophy [5].

It is also known that this molecular structure can explain the main side effects of isotretinoin. Excessive activation of p53 and FoxO1 in embryonic neural crest cells causes their apoptosis and is one of the molecular reasons for teratogenicity [5, 8]. Too much activation in hippocampal neurons can harm neurogenesis and is thus associated with depression [5]. P53 and FoxO1 in hepatocytes increase the production of apolipoprotein B (APOB) and apolipoprotein C3 (APOC3) to raise very-low-density lipoprotein (VLDL) synthesis and reduce its removal; therefore, there is hypertriglyceridemia [5]. p53 in epidermal keratinocytes promotes the expression of AQP3 and thus causes dry skin. p53 in choroid plexus epithelial cells upregulates aquaporin 1 (AQP1), and it has been proposed that this may be associated with elevated intracranial pressure [5].

4. Current Situation of Clinical Application and Evidence-Based Evaluation

4.1 Clinical Effect

Isotretinoin is currently one of the few drugs that can address all four links in the pathology of acne simultaneously and has shown good clinical results. At the usual dose of 0.5-1.0 mg/kg/d, it has been found that about 77%-89% of severe nodulocystic acne lesions can be cleared [1]. It has a relatively short onset of action; after about 4 weeks of treatment, most of the spots will be gone, and some patients have maintained this state for a long time [1]. In addition to a reduction in the number of lesions, isotretinoin can also significantly lower the levels of certain pro-inflammatory cytokines in the blood, such as TNF-α, IL-4, IL-8, IL-17 and IFN-γ; thus, it may also reduce inflammation throughout the body [5]. For a longer period, if the total dose exceeds 220 mg/kg, the recurrence rate at 1 year will drop from 47.4 per cent to 26.9 per cent; thus, it is suggested to increase the total dose and extend the time of remission [1]. A low dose of less than 0.5 mg/kg/day can also treat mild acne and rosacea [11]. In short, although isotretinoin can effectively control lesions, reduce inflammation, achieve long-term remission, and other advantages, its effects on people's mental health have not yet been studied in many cases, so more research is needed.

4.2 Dosage Strategy

Based on the first study, it was proposed that the accumulated dosage would be 120-150 mg/kg; however, comprehensive reviews in recent years have been less conclusive about this [10]. At present, most people have been treated individually based on their own circumstances and clinical outcomes, so they continue taking the standard dose to completely clear the lesion, and then there is a one-month consolidation period [1]. Patients with serious trunk tumours or a high risk of recurrence will be prescribed a relatively large total dose of the drug to reduce the risk of recurrence [1].

ISSN 2959-409X

Low-dose regimens (≤0.5 mg/kg/d) are used in some groups of people. Moderate acne patients can be treated well and are unlikely to have serious side effects [1]. Low-dose isotretinoin is also a first-line and second-line drug for the papulopustular type of rosacea [11]. A very small amount (5-10mg/day) can be used for a long time to control recurrence [11].

4.3 Combined Treatment

The combination treatment of isotretinoin is mainly laser/phototherapy. Meta-analysis of the 6 studies with 285 patients found that combined therapy was better than single-agent therapy in terms of the proportion of clinical improvement and total lesion reduction, and it did not increase the risk of scarring or pigmentation [12]. It can be applied to the difficult cases of acne scars or those that do not respond to monotherapy. In addition to phototherapy, doxycycline can also be taken orally to reduce inflammation before the start of the effects of isotretinoin and lower the risk of early deterioration [1]. Combination of topical isotretinoin or benzoyl peroxide for maintenance treatment can reduce the recurrence and prolong the time of remission [1,2]. Overall, the clinical improvement effect of the combined treatment of isotretinoin is clearly superior to monotherapy; that is to say, it can better control inflammatory lesions and prevent recurrence safely.

4.4 Safety and Side Effect Management

The typical side effects are dry skin and mucous membranes, myalgia, headache, etc.; they are associated with the dose and can be treated by informing the patient and treating symptoms [2]. In the field of lab monitoring, it is suggested that healthy patients have their blood lipid and liver function tests conducted at the start and in the second month after treatment. GGT is more characteristic of the liver than aminotransferases and therefore requires attention. Mild or moderate hypertriglyceridemia can be managed by way of life changes and omega-3 fatty acid supplements. If it is more than 500 mg/dL, the dose needs to be reduced or the drug should be stopped [2].

Teratogenicity is still an absolute contraindication for the other side effects. Pharmacokinetic studies have shown that the concentration of the drug in the blood can drop to the level of endogenous substances after one month of taking the drug, and thus are safe [6]. Many studies have not found that isotretinoin is associated with an increase in the risk of depression. Acne can cause depression, and the depression score is usually lower after treatment [1,2]. Recent studies have not been able to find a direct link between isotretinoin and inflammatory bowel disease (IBD), but there is a stronger correlation with oral antibiotics [1,2].

According to a cross-sectional study, only 27.6 per cent of general practitioners in primary care prescribe isotretinoin; their reasons are that it can harm the liver, cause birth defects, or they are not familiar with the drug [9]. Therefore, at the grassroots level, the strengthen training and develop national guidelines are needed to improve drug coverage [9].

5. Future Perspectives and Conclusion

In recent years, advances in transcriptomics and molecular biology have helped improve the understanding of both acne pathogenesis and the therapeutic effects of isotretinoin. Increasing evidence suggests that overactivation of the IGF-1/PI3K/AKT/mTORC1 pathway, together with reduced nuclear activity of p53, FoxO1, and FoxO3, plays an important role in excessive sebum production, abnormal keratinisation, and inflammatory responses. After being converted into all-trans-retinoic acid, isotretinoin can activate RAR-related signaling pathways and partially reverse this transcriptional imbalance, which may explain its anti-inflammatory and sebosuppressive effects in acne treatment.

Clinical studies continue to support isotretinoin as one of the most effective therapies for severe acne. At the same time, low-dose regimens and combination therapies appear to provide better tolerability and may help maintain long-term disease control. Although adverse effects such as teratogenicity and lipid abnormalities still require careful monitoring, current evidence has not established a definite causal relationship between isotretinoin and depression or inflammatory bowel disease.

Looking ahead, future research may focus more on improving drug delivery and reducing systemic toxicity through approaches such as nanoparticle formulations, selective retinoic acid receptor targeting, and optimized long-term maintenance strategies. More individualized treatment plans based on disease severity, recurrence risk, and patient response may also help improve clinical outcomes. Overall, continued integration of molecular research and clinical evidence is expected to further refine the use of isotretinoin and support its broader application in dermatology.

This review still has some limitations. Although recent molecular and transcriptomic studies were included, some mechanisms of isotretinoin remain unclear and still need more clinical evidence. In addition, several studies discussed in this article had relatively small sample sizes or limited follow-up periods. More large-scale and long-term studies are still needed to better evaluate the safety and personalised use of isotretinoin.

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