Clinical Implications of Associations between Genetic Mechanisms and Oral Isotretinoin Therapy: A Review of Literature

Luka Bulić[1], Eva Brenner[1], Nives Pustišek[2,3], Suzana Ožanić Bulić[2,3]

[1] School of Medicine
University of Zagreb
Zagreb, Croatia

[2] Department of Pediatric Dermatology
Children's Hospital Zagreb
Zagreb, Croatia

[3] School of Medicine
Catholic University of Croatia
Zagreb, Croatia

Luka Bulić
luka.bulic0302@gmail.com
ORCID: 0000-0001-6522-891X

Eva Brenner
eva.brenner13@gmail.com
ORCID: 0000-0002-6638-2967

Nives Pustišek
nives.pustisek@kdb.hr
ORCID: 0000-0002-2401-9238

Suzana Ožanić Bulić
suzanaozanic@hotmail.com
ORCID: 0000-0002-1871-826X

Corresponding author:
Suzana Ožanić Bulić
Department of Pediatric Dermatology
Children's Hospital Zagreb
Ul. Vjekoslava Klaića 16
Zagreb, Croatia
suzanaozanic@hotmail.com

Abstract

Isotretinoin (13-cis-retinoic acid) is a vitamin A derivative most commonly used for the treatment of acne vulgaris. While its therapeutic effectiveness in this skin condition has been demonstrated by numerous studies, oral isotretinoin therapy impacts many other organ systems by interacting with complex genetic mechanisms. Epigenetic modifications make up a large portion of these interactions and they entail induction or suppression of specific gene expressions. While gene expression modification has been shown as important for the mechanism of action of isotretinoin, it is also deemed responsible by some for certain adverse events. Studies have postulated associations between isotretinoin and inflammatory bowel disease (IBD), autoimmune thyroiditis, and skeletal system diseases in the context of specific genetic predispositions. Isotretinoin has also been shown to negatively affect the glucose and lipid metabolic profile via these interactions. Furthermore, it can alter the therapeutic effect of other drugs by modulating the activity of their metabolizing enzymes. On the other hand, isotretinoin has shown anti-tumor activity and a positive effect in anthracycline cardiotoxicity. The other relevant component of genetic factors in isotretinoin therapy is pharmacogenetics, which entails genetic products that take part in isotretinoin metabolism. Variants in these genes alter the mechanism by which the body metabolizes isotretinoin, which can cause therapeutic ineffectiveness or toxicity depending on the variant. The aim of this review was to provide a synthesis of knowledge regarding these interactions and potentially contribute to individualized isotretinoin therapy based on certain genetic findings.

Keywords: epigenetics, isotretinoin, metabolism, pharmacogenetics

1. Introduction

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit caused by obstruction of hair follicles. It is estimated that this condition affects up to 9% of the world population and is generally one of the most common skin conditions. While the condition does not affect other organ systems and presents little threat to overall health, it has significant psychosocial implications and can negatively impact quality of life. Potential therapeutic options include topical treatment, such as benzoyl peroxide and topical retinoids, or systemic treatment, such as hormone-based therapy, doxycycline, and oral isotretinoin (1).

Isotretinoin, or 13-cis-retinoic acid, is a vitamin A derivative approved for the treatment of severe acne by the Food and Drug Administration in 1982. Since the beginning of its use, isotretinoin has proved great efficacy in the treatment of acne, including moderate, and severe lesions like acne conglobata (2). Many studies have investigated the effectiveness of isotretinoin therapy and concluded that it is an effective agent against acne (3). On the other hand, some meta-analyses call isotretinoin treatment effectiveness into question and suggest it still requires further investigation (4). Alongside acne vulgaris, isotretinoin has been used off-label in the treatment of many other skin conditions. These include psoriasis, pityriasis rubra pilaris, rosacea, granuloma annulare, hidradenitis suppurativa, and even neoplastic skin diseases such as non-melanoma skin cancer and cutaneous T-cell lymphoma. As expected, the effective dose varies depending on the condition being treated (5).

Over the last decade, a growing new concept in healthcare has been personalized medicine, which implies individualized treatment for each patient based on their biomolecular profile. Biomolecular profiling is closely related to MULTI-OMICS analysis, which entails genomics, transcriptomics, proteomics, metabolomics, glycomics, etc. Regarding genomic medicine, an essential tool, widely used today in both research and clinical medicine, is whole genome sequencing (WGS) (6). Using WGS technology, an unimaginably wide range of genetic variants can be discovered, leaving the crux of the issue in their interpretation. Pharmacogenomics is a specialized branch of genomic medicine that focuses on how genetic variants in specific genes can affect the relationship between a drug, or more specifically, its dose, and its therapeutic effect. The goal of this research is to facilitate the creation of personalized therapeutic guidelines for each drug, dependent on the patient's genetic profile (7).

The relationship between systemic isotretinoin therapy and genetics has been established in the literature. On the one hand, isotretinoin impacts existing genetic mechanisms through epigenetic modifications. On the other hand, certain genetic variants in genes involved in isotretinoin metabolism impact its therapeutic effect (Figure 1).

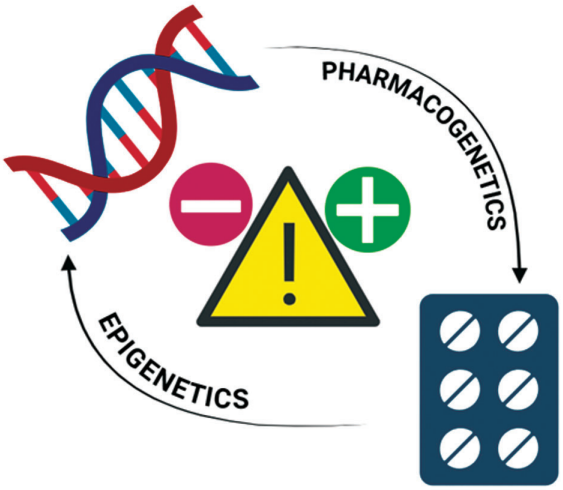

Figure 1. *Graphical representation of the relationship between isotretinoin and genetics (created with Biorender.com)*

The aim of this review is to provide a synthesis of knowledge produced by studies which investigated these relationships. These findings should be highlighted as they are crucial for the development of personalized guidelines for isotretinoin therapy administration.

2. Epigenetic modifications related to systemic isotretinoin therapy

The impact of systemic isotretinoin therapy on epigenetic mechanisms has been thoroughly researched. Many such examples have been discovered and published, pertaining to multiple genes and organ systems. While these mechanisms do account for certain adverse events, positive modifications have also been discovered, pointing to other possible uses for this medication.

2.1. Expression modulation associated with mechanism of action

Zhang et al. investigated the effect of systemic isotretinoin therapy on the meibomian gland secretory function in a rat model (8). After a significant period of systemic therapy administration, the authors measured the expression levels of several genes and associated products, including *PPARγ, FoxO1, FoxO3, IL-6,* and others. Upregulation of expression of inflammatory genes was not detected but a significant suppression of the PPARγ pathway was noted. This was associated with meibomian gland dysfunction as a result of differentiation abnormalities caused by the PPARγ alterations. The study by Nelson et al. investigated gene expressions altered by isotretinoin in a large number of genes and genetic loci (9). Findings after a certain period of treatment found that expressions of nearly 200 genes had been increased and that expressions of nearly 600 genes had been decreased. The domains of increased expression included genes such as collagen and fibronectin, while domains of decreased expression included steroid metabolism enzymes, as well as genes related to other metabolic pathways. The effect of isotretinoin on sebaceous glands was confirmed, as treatment caused functional impairment within 2 weeks and anatomical reduction of the glands within 8 weeks. The authors concluded this was a result of cell cycle arrest and apoptosis induction caused by specific epigenetic modifications.

2.2. Expression modulation associated with specific organ-system adverse effects

Migdad et al. investigated the associations between systemic isotretinoin therapy and inflammatory bowel disease (IBD) (10). While findings showed that there is no general significant association between isotretinoin and IBD, a possible risk of ulcerative colitis development was noted in patients who were highly susceptible to the disease. One interesting theory behind this, which was presented in the article, was an increased expression of *a4β7* and *CCR9* genes in T-cells activated by isotretinoin, which greatly impacts the inflammatory response in the gastrointestinal system. Becker et al. also investigated the association between IBD and isotretinoin (11). Findings showed induced IL-10 signaling in Treg cells and naïve T-cells, with reduced proliferation of T-cells. A case report by Nugroho and Schweiger presents systemic isotretinoin therapy as a potential trigger for autoimmune thyroiditis in patients with genetic predispositions (12). The explanation the authors present entails alteration of TSH expression through dimerization of the RXR nuclear receptor with RAR and thyroid nuclear receptors. A report published by Lamb et al. postulates the association between KRT10 variants, systemic isotretinoin therapy, and adverse events related to the musculoskeletal system such as skeletal hyperostosis and avascular hip necrosis (13).

2.3. Expression modulation associated with altered metabolic profile

Sedova et al. published a study in which the effect of systemic isotretinoin on the metabolic profile of the insulin resistance rat model was investigated (14). Increased expressions of the *ApoC-III* and *Hnf-4* genes were detected in isotretinoin-treated rats. Regarding the metabolic profile, increased peripheral insulin resistance and glycerol concentrations were detected. Interactions of isotretinoin with pharmacogenetic mechanisms of other drugs have also been noted. Another study, published by Khabour et al., investigated lipid profile changes with specific leptin (*LEP*) gene variants in

patients on systemic isotretinoin therapy (15). Significant changes in lipid profile included an increase in LDL cholesterol, total cholesterol, and triglycerides, and a reduction in HDL cholesterol. Additionally, liver enzymes AST and ALT were significantly increased. The aforementioned changes in metabolic profile were associated with the *LEP* rs7799039 polymorphism. Similarly, associations between isotretinoin and adiponectin (*ADIPOQ*) variants and their effect on the metabolic profile have also been investigated. Garba et al. found a significant impact of the *ADIPOQ* rs1501299 polymorphism on HDL cholesterol levels in patients on systemic isotretinoin treatment (16).

2.4. Expression modulation of genes involved in drug metabolism

A study by Zhao et al. investigated the effect of isotretinoin on the activity of different genes involved in drug metabolism (17). Findings showed suppression of *CYP2D6* activity and induction of *CYP3A* and *UGT2B* activity. Interference with *CYP2D6* activity can cause adverse events in patients using psychotropic drugs, such as amitriptyline or desipramine, and cardiac-related drugs, such as metoprolol, flecainide, or propafenone (18). Similarly, *CYP3A* modifications can cause undesirable interactions with immunomodulators, macrolide antibiotics, calcium channel blockers, antiepileptic drugs, benzodiazepines, and others (19).

2.5. Expression modulation with a positive impact on other diseases

A study by Agamia et al. investigated correlations between systemic isotretinoin and *p53* expression (20). After six weeks of therapy, the expression of *p53* was found to be significantly increased. By modulating *p53* expression, isotretinoin indirectly affects several other transcription mechanisms, such as *FoxO1*, the androgen receptor gene, and genes critical for apoptosis and autophagy. These epigenetic modifications are in line with morphological and functional changes noted in sebaceous glands. It has also been shown that isotretinoin negatively affects *c-MYC* promoters in hepatocytes, leading to the suppression of the gene (21). This presents a potential use of isotretinoin for oncogene expression modulation in hepatocellular carcinoma. A similar anti-tumor effect was found in human neuroblastoma cells in a study published by Sonawane et al. (22). Isotretinoin and its metabolite 4-oxo-13-cis-retinoic acid were shown to reduce the expression of the *MYCN* gene and increase the expression of *RARβ*. *MYCN* is a proto-oncogene that plays a key role in the genetic pathogenesis of neuroblastoma and is one of the potential targets in trials for individualized cancer therapy (23, 24). Additionally, isotretinoin has been shown to affect the expression of topoisomerase IIβ in medulloblastoma cells, an enzyme that has a crucial role in neuronal differentiation (25). An article by Ma et al. discusses the potential of systemic isotretinoin use in anthracycline-induced cardiotoxicity (26). The underlying mechanism is the regulation of tight junction protein ZO-1 expression via activation of the retinoic receptor RXRA, which stimulates the repair of damaged endothelium.

3. Pharmacogenetic factors related to systemic isotretinoin therapy

Genetic polymorphisms in certain genes can affect how the body metabolizes orally administered isotretinoin. These metabolic alterations can lead to deviations from the expected dose-effect relationship. On the one hand, fast metabolizers might experience therapeutic ineffectiveness, as a higher dose of the drug might be necessary to reach the same effect. On the other hand, slow metabolizers may experience toxic side effects, due to increased amounts of the drug in the bloodstream than expected. Alongside enzyme genes, transporter and receptor gene polymorphisms can also negatively impact therapeutic effectiveness (7). Studies have investigated which genes take part in isotretinoin metabolism and might contribute to unwanted effects.

The advantages of pharmacogenetic polymorphism testing in the case of systemic

isotretinoin therapy are highlighted in the article published by Veal et al. (27). Alzoubi et al. studied how three polymorphisms (rs9303285, rs2715554, and rs4890109) in the retinoic acid receptor alpha (*RARA*) gene affect therapeutic effectiveness (28). Side effects such as headaches, epistaxis, myalgia, and arthralgia were associated with CTG and TTG three-locus haplotypes. Headaches and epistaxis were also associated with the TCG three-locus haplotype, while arthralgia and myalgia were associated with the TTT three-locus haplotype. Additionally, increased AST levels were associated with the rs2715554 TC genotype, while the rs9303285 T allele had a protective effect regarding depression. An article published by Ross and Zolfaghari discusses the genes and enzymes involved in retinoic acid metabolism (29). The *CYP26* family is highlighted, including *CYP26A1*, *CYP26B1*, and *CYP26C1*. Alongside its essential role in embryonic development, the article points out the importance of *CYP26A1* in retinoic acid clearance and proposes that limiting *CYP26* activity might be a viable way to extend retinoic acid half-life. However, a study by Wang et al., which investigated how *CYP26* activity affects isotretinoin therapeutic effectiveness (30), showed that the impact was not significant. Gota et al. also investigated this matter, taking into account polymorphisms of *UGT2B7*, *CYP3A5*, *CYP3A7*, and *CYP2C8* (31). The authors also found no effect of the tested polymorphisms on isotretinoin pharmacokinetics. The aforementioned study by Sonawane et al. found that *CYP3A4* plays a major role in isotretinoin metabolism, more accurately its catalysis to 4-oxo-13-cis-retinoic acid (22). With the previously mentioned inducing effect that isotretinoin has on the *CYP3A* family, this suggests a two-sided impact between the two factors (17).

4. Conclusion

The scientific evidence provided in this review demonstrates a strong association between various genetic factors and orally administered isotretinoin. Findings suggest that genetic testing might be beneficial prior to oral isotretinoin therapy initiation. A panel of selected genes, which are proven to interact with this drug, would potentially discover any risk-associated variants and aid in avoiding adverse events by dose modulation or alternative therapy selection. On the other hand, the study of genetic associations has led to other potential indications for this drug, an excellent example of which is its anti-tumor activity. However, before these various findings are implemented into clinical practice in the form of individualized guidelines or other, further research is needed and a consensus must be made among the experts.

Declarations

Authors' contributions

All the authors have contributed equally to this work and have read and approved the final version of the manuscript.

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Competing interests

The authors declare no conflict of interest.

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