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13-*cis*-Retinoic Acid: It's Therapeutic Implications and Adverse Effects

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A R T I C L E I N F O

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A B S T R A C T

Isotretinoin (13-*cis*-retinoic acid) is a second-generation synthetic retinoic acid analog beneficial for the treatment of recalcitrant nodulocystic acne. The 13-*cis*-retinoic acid is also used to treat oral leukoplakia and has shown mixed results in cancer therapy. It is a much safer drug but can cause severe side effects like teratogenicity, dryness of the skin (including eyes, tongue, mouth, and nasal mucosa), rashes on the face and body, itching, increased photosensitivity, bleeding from the nose (epistaxis), lip inflammation (cheilitis), bleeding & inflammation of gums (gingivitis), and depression & suicidal ideation in patients. It is a schedule H drug and is contraindicated in pregnant women. This review article gives a complete understanding of the pharmacology of Isotretinoin along with the completed clinical trials and research on Isotretinoin for treating other diseases apart from acne and oral leukoplakia. The article also deals in measures to prevent the adverse effects related to 13-*cis*-retinoic acid.

KEYWORDS: Retinoids, Isotretinoin, Retinoic acid receptors, Acne, Oral leukoplakia, Teratogenic effect, Mucocutaneous effect, Triglycerides, Psychological effect, Cancer therapy, Clinical trials, Schedule H drug

Introduction

Retinoids belong to the polyisoprenoid family of lipids which include the natural and synthetic analogs of Vitamin A (**Figure 1**). Retinoids are antioxidant compounds, and they are responsible for maintaining the equilibrium among cell proliferation, growth, embryonic development, and death. [1][2] Retinoids are classified into three generations, according to their chemical structure as non-aromatic retinoids, monoaromatic retinoids, and polyaromatic retinoids (arotinoids). The first-generation Retinoic acid analogs include *trans*-retinoic acid and 13-*cis*-retinoic acid. The second-generation Retinoic acid analogs include Alitretinoin, Etretinate, and Acitretin. The third-generation retinoids are polyaromatic (arotinoids): adapalene, tazarotene, and bexarotene. [3] Aromatic retinoids include Ro11-1430, known as Tasmaderm, which is used in the treatment of Ichthyosis Vulgaris. [4]

Isotretinoin (13-*cis*-retinoic acid) is a synthetic retinoid widely used for oral treatment of recalcitrant nodulocystic acne and severe keratinization disorders that do not respond to traditional acne therapy. The Food and Drug Administration has approved Isotretinoin since 1982. Isotretinoin decreases the proliferation of basal sebocytes, suppresses sebum production, and inhibits differentiation of sebocytes. This helps in reducing sebaceous gland size up to 90%. It is a SCHEDULE-H drug and is contraindicated in pregnant women as it is highly teratogenic by nature. Isotretinoin has been reported to have adverse events like depression and suicidal ideation in patients. [5][6][7] This review article deals with a detailed analysis of the therapeutic effects and adverse effects of systemic 13-*cis*-retinoic acid therapy in humans.

History of 13-*cis*-retinoic acid[8][9]

The 1960s to 1970s

In the 1960s, Isotretinoin was initially studied for the treatment of skin cancer by Werner Bollag. This study was carried out at the Department of Experimental Medicine, Hoffman-La Roche laboratories, Basel, Switzerland. He found isotretinoin to have no therapeutic value in cancer treatment and discarded the drug to be used as a pharmaceutical. However, during the study, in 1971 he discovered the compound's ability to treat acne. In 1975 Gary Peck and Frank Yoder in the US rediscovered isotretinoin's therapeutic effects for the treatment of cystic acne. In 1979 Hoffman-La Roche registered isotretinoin as Accutane with the US Food and Drug Administration (FDA) in Maryland.

Entire 1980s

During August of 1983, Franz Rosa, working for the US FDA in Maryland, published an article describing twelve Accutane-related cases of embryotoxicity. In response, Hoffman-La Roche distributed red warning stickers to pharmacies for Accutane. It also revised Accutane's drug label to include more information about the possibility of congential disabilities. On February 11, 1988, Several members of the FDA's Dermatologic Drugs Advisory Committee advocated that Accutane be taken off the market, citing estimates that it has impacted anywhere from 900 to 1,300 infants in the United States. After reported

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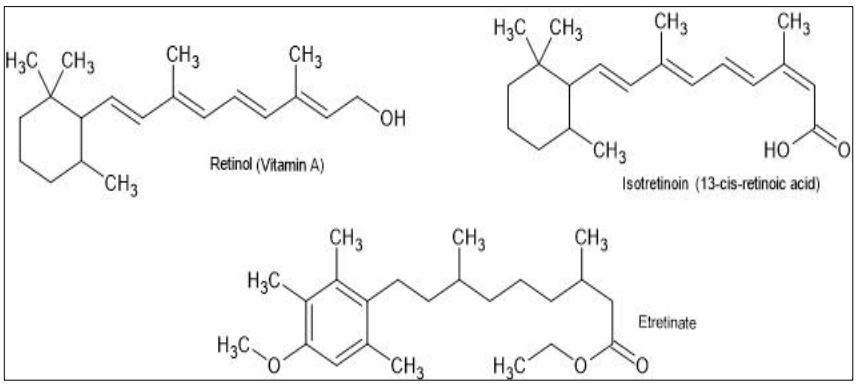

Figure 1: Type of Retinoic Acid Analogues (Drawn through Chemsketch 2.0).

meetings with the committee members in the subsequent months, the FDA issued new label warnings for Accutane instead of taking the drug off the market as per the committee's recommendation. FDA told Hoffman-La Roche to implement a Pregnancy Prevention Program (PPP) for Accutane on October 1988.

Entire, 1990s

Hoffman-La Roche battled with the ramifications of Accutane's teratogenicity. The pharmaceutical company was involved in multiple court cases in Ohio and New Jersey related to the teratogenicity of Accutane.

2001 to 2012

In 2001 Ranbaxy got US FDA approval for Isotretinoin. On June 21, 2002, Isotretinoin capsule 10mg/20mg was approved by CDSCO, India for treatment of cystic and conglobate acne, severe nodular acne. Ranbaxy in 2003 announces FDA approval for the manufacture and commercialization of Isotretinoin Capsules. On March 1, 2006 The FDA instituted the pledge program where US patients using Accutane must enroll in this risk management program designed to prevent fetal exposure to isotretinoin. In 2012 Ranbaxy Launched Absoricatm (Isotretinoin) Capsules In The U.S. Healthcare Market.

July 26, 2018

Indian Drug Regulatory Body, CDSCO, after consulting with the Subject Expert Committee(Dermatology and allergy) directed the manufacturers to include a warning label as " The drug should be sold by retail on the prescription of Dermatologists only".

Also, the manufacturers were directed to include a boxed warning that said "*This medicine may cause severe birth defects. You must not take this medicine if you are pregnant or may likely become pregnant during the treatment. You should also avoid pregnancy for 6 months after stopping the treatment.*"

PHARMACOLOGY OF ISOTRETINOIN

Isotretinoin reduces sebum production up to 90% by inhibiting sebaceous lipid synthesis. Sebaceous gland activity and keratinization are impaired by isotretinoin when delivered at pharmacologic dosages of 0.5 to 1.0 mg/kg/day. Isotretinoin reduces the sebaceous gland size by decreasing the proliferation of basal sebocytes. [10] However, the proper pharmacological mechanism of action of Isotretinoin is not yet understood completely. It is believed that *13-cis- retinoic acid*exerts its action by isomerization to all-*trans*-retinoic acid, which then interacts with the retinoid receptors. The retinoid receptors bind in the form of dimers to their ligands. The retinoid can show agonistic behavior, but it can also be neutral antagonists and inverse agonists. [3] There are two classes of retinoid receptors, RAR and RXR, each of which is recognized by three subtypes (alpha [α], beta [β], and gamma [Y]). Numerous synthetic and endogenous retinoid receptor-binding ligands have been identified, showing differing affinities for these receptors. The term "rexinoid" has been coined to refer to selective compounds for RXR, and it has been proposed that the word "retinoid" be reserved for ligands that bind RAR. RAR is the receptor for *all-trans* retinoic acid, and RXR is the receptor for *9-cis* retinoic acid. According to the scientist Chambon, RXR can either form homodimers or heterodimerize with other ligand-bound nuclear receptors, such as RAR, PPAR, vitamin D receptor, thyroid hormone receptor, or "orphan receptors." Orphan receptors are mainly those receptors for which there is no known endogenous ligand. [6] On the other hand, isotretinoin (*13-cis-retinoic acid*) has little or no ability to attach to retinol-binding proteins or retinoic acid nuclear receptors in the cell (RARs and RXRs). It could function as a prodrug that is metabolized intracellularly to serve as agonists to RAR and RXR nuclear receptors. Only tretinoin and 4-oxo-tretinoin bind to the RAR- receptor, which is significant in retinoid acne treatment. [11]

The pharmacokinetic profile of Isotretinoin reveals that < 50% is absorbed from the gut, and 25% of the absorbed drug is converted to tretinoin (active form). The rest of the not consumed substance is oxidized and/or conjugated and excreted in bile. It is highly bound to plasma protein and is metabolized to 4-oxo-isotretinoin. The five biologically important metabolites of Isotretinoin include 13-*cis*-4-oxo-retinoic acid (4-oxo-isotretinoin), all-*trans*-retinoic acid (tretinoin), all-*trans*-4-oxo-retinoic acid (4-oxo-tretinoin), 9-*cis*-retinoic acid, and 9-*cis*-4-oxo-retinoic acid. The plasma half-life is greater than or equal to 24 hours, but some metabolites persist for 1-2 months. [1][49] Nulman et al. found a prolonged elimination half-life in one female patient of about 167.4 hours when they conducted a study of sixteen young adults to determine the period required to reach safe levels after using isotretinoin. The study concluded that 35 days would be necessary to achieve safe levels and requires a minimum of 5 half-lives. [7] Isotretinoin is detectable after 30 min in blood, and maximum concentrations are reached 2–4 hours after oral intake. Isotretinoin is advised to be taken immediately after eating food at the same time of the day. The absorption of Isotretinoin is doubled in the fed state rather than the fasting state. [12] [49] Isotretinoin is not effective topically. Isotretinoin is a crystalline powder orange in color, soluble in chloroform, and insoluble in water. The melting point is approximately 175ºC; pKa around 4. In India, Isotretinoin is marketed as soft gelatin capsules and is available in the strength of 10mg, 20mg, and 40 mg.

Therapeutic effects of Isotretinoin

Isotretinoin is a retinoid that can prevent complications related to Acne Vulgaris. It counteracts the pathogenic factors that contribute to the development of acne and acts as an anti-inflammatory drug. Isotretinoin reduces chemotaxis and migration to the epidermis of monocyte and neutrophil. This helps to minimize the excessive inflammation that causes scarring. [12]

Acne is a chronic pilosebaceous inflammatory condition clinically characterized by comedones, papules, pustules, nodules, cysts, and scarring (in some cases). It is the most prevalent dermatological disease that affects about 85 % of people between 12-24 years. Isotretinoin is considered the only drug that affects the four pathogenic factors of acne: hyperkeratinization, abnormal keratinization of the infundibular epithelium leading to blockage of sebaceous follicles, excess sebum production, and formation of microbial colonies by the bacteria Cutibacterium acnes leading to perifollicular inflammation.

It reduces the secretion of Sebum and Sebaceous gland and affects the oil skin status. [5][13][14]

In a study carried out by Uma Shankar Agarwal et al., the efficacy and tolerability of various regimens of oral isotretinoin were compared. The study also assessed the usage of oral isotretinoin in mild and moderate acne. A total of 120 acne patients were randomly assigned to one of four treatment regimens, each comprising 30 patients. Group A (1 mg/kg/day), Group B (1 mg/kg alternate day), Group C (1 mg/kg/day for one week/four weeks), and Group D (20 mg every alternate day) for 16 weeks. Side-effects were recorded in the course of 16 days of follow-up. Patients with a dose of 1 mg/kg daily performed better at eight weeks, but at 16 weeks, the results became similar with the patient taking 1 mg/kg alternate day (group B) and 20 mg every alternate day (group D). Patients taking a dose of 1 mg/kg daily performed better in severe acne. They had considerably more frequent and severe treatment-related adverse effects than patients taking lower/less regular doses (Groups B, C, and D). Patients with mild acne recovered well in all the groups, although those with moderate acne did better in Groups taking dose 1 mg/kg daily, 1 mg/kg alternate day, and 20 mg every alternate day (i.e., Group A, B, and D). Thus, conventional high dose isotretinoin or at least at the initial stage of the treatment is considered suited for severe acne. The low dose of isotretinoin is deemed to be suited for mild acne. [15]

Similarly in another study carried out by Dr. Hemant Vasant Talanikar and his team, the clinical efficacy and side effects of oral isotretinoin was determined when it was given as a daily conventional-dose and fixed low-dose therapy in moderate to severe acne patients. [16] In that prospective randomized comparative study, about one hundred individuals with moderate to severe acne were randomized into two groups of 50 patients each, based on the severity of their acne (mild, moderate, and severe). Group A received 0.5 mg/kg/day of oral isotretinoin, while group B received a fixed dose of 5 mg/day. Every four weeks until 16 weeks, a follow-up was performed. On each visit, the total acne load, side effects, and laboratory tests were documented. [16]

Total Acne Load at weeks	Mean % change (SD)	
	Group A	Group B
4	49.68 (15.43)	34.20 (12.51)
8	82.04 (10.36)	59.76 (11.5 6)
12	94.86 (6.22)	80.64 (10.49)
16	99.16 (1.57)	90.91 (7.17)

Group A: n=50, F-Value=117.22, p<0.0001; Group B: n=50, F-Value=163.53, p<0.0001

Table 1: Comparison of percentage change in Total Acne Load at different weeks in group A and group B[16].

The mean percentage decrease in overall acne load was 99.16 % in group A and 90.91 % in group B at the end of treatment (Table 1) There was a statistically significant difference (p<0.0001) in terms of reduction in total acne load, grade of acne improvement, and response to a reduction in the number of lesions in both groups. Group A did better, with about three-quarters of the patients being cured, the remaining one-fourth being shifted to a low grade, and none of the patients having moderate or severe acne at the end of treatment. In Group B, less than a quarter study population healed completely. However, the overall outcome at the end of therapy was positive in both groups since neither group had any patients with severe acne by the end of the 12 weeks. Cheilitis was the most common adverse effect. It was discussed that; Isotretinoin should be started early in the treatment of acne; even low-dose isotretinoin (0.25–0.5 mg/kg/day for 24 weeks) offers a fair balance of effective dose-related side effects. Low-dose isotretinoin regimens for different durations have been explored to reduce side effects and enhance patient medication adherence. Overall, it was concluded that fixed low-dose oral isotretinoin is nearly as effective as a daily conventional-dose regimen with the added benefits of fewer side effects, increased patient compliance, and cost-effectiveness. Still, it must be given for a more extended period in severe acne and is associated with a risk of relapse. [16]

Isotretinoin is also used in the treatment of oral leukoplakia, a white lesion in the oral mucous membrane that has the potential for malignancy. [2] [17]

A study of 26 individuals treated with topical 0.05 % tretinoin gel four times a day for 3.5 years found that 27 % of the study population achieved complete remission, and 40% experienced a recurrence of the disease after stopping the treatment. Another study with 0.1% *13-cis- retinoic acid*gel thrice a day showed partial remission. Other studies suggest low dosages of *13-cis- retinoic acid*(0.5 mg/kg/day) when given topically for more extended periods have less toxicity and are related to decreased recurrence rates after complete treatment or discontinuation. Overall, topical retinoids are seen as safe, convenient, and effective for treating oral leukoplakia, with fewer side effects than systemic retinoids. There are currently no therapeutic guidelines for the use of retinoids and other vitamin A derivatives. To determine the safety and efficacy of retinoic acid in treating oral leukoplakia, controlled clinical trials are required. [17]

Piattelli et al. carried out a pilot study to determine the effect of topical 13-*cis*-retinlic acid for treating oral leukoplakia. [18] This study monitored the expression of bcl-2 protein and apoptotic bodies in *13-cis- retinoic acid*(isotretinoin)-topically treated oral leukoplakia. Patients were given topical 0.1% isotretinoin gel (Roaccutane, Roche) or plain gel (placebo) in a double-blind study. For four months, patients applied the gel topically to the affected mucosal areas three times each day. All patients were assessed each month. A total of 9 patients completed the study. During the double-blind phase, all patients who received isotretinoin gel demonstrated an improvement in their oral lesion after four months, but those who received placebo showed almost no change.

The study resulted in one complete recovery and eight partial recoveries. There were no reports of adverse effects from using the gel. An increase in apoptotic bodies was detected, with fragmented and pyknotic nuclei and eosinophilic cytoplasm in the basal layers. Only two samples had apoptotic bodies in the apical layers. Statistical analysis revealed that the difference in bcl-2 positivity between the two groups was not statistically significant (P=0.134), while the difference in apoptotic body count between the two groups was statistically significant (P=0.0193). Hence it was concluded that good results could be obtained with the topical use of *13-cis-retinoic acid*. Isotretinoin has also been beneficial for treating hidradenitis suppurativa (HS), Darier's disease, granulomatous rosacea, and several congenital ichthyoses. [18]

Isotretinoin has also been used to treat various bone marrow cancers and neuroblastoma. [19] Isotretinoin is the medication of choice in young patients with xeroderma pigmentosum because of its short half-life. [20]

The therapeutic effect of Isotretinoin for Cancer treatment

The use of Isotretinoin as an anti-cancer agent is revolutionary. It has proved to be effective in chemoprevention and suppression by modulating growth, cell differentiation, and apoptosis induction. Treatment with Isotretinoin in lower doses has always been seen to treat skin lesions induced by the epidermal growth factor receptor (EGFR)-blocking agent Cetuximab. [21] In the 1990s, isotretinoin was utilized in the uptake of radioiodine for patients with thyroid cancer. However it did not show a high statistical improvement in thyroid cancer. [22] [23]

Retinoid therapy is efficient in preventing pre-malignant lesions and prevents the tumour from proliferating and reaching a severe stage. The mechanism suggests that retinoid therapy restores the lowering of nuclear retinoid receptor beta (RAR beta) in premalignant dysplastic lesions and encourages normal growth and differentiation of epithelial cells. The combination of 13-*cis*- retinoic acid with 5-fluorouracil 20mg/day shows an increase in cell apoptosis and inhibition in the line proliferation of oral squamous cell carcinoma (SCC). Isotretinoin in combination with chemotherapy, total skin electron beam (TSBE), Psoralen UltraViolet A (PUVA) therapy, and INF-α is an effective therapeutic technique to treat Cutaneous T-cell lymphoma (CTCL). Isotretinoin in 1mg/kg/day combined with INF-α is effective in suspending stage I and II CTLC for as long as 18 months.[24] Oral monotherapy in 0.5-2mg/kg/day dose showed lesion clearance for two to three months, whereas combination therapy in 0.5-1.5mg/kg/day showed the same results for three to four months.[25]

The treatment with Isotretinoin has been proved to be beneficial in high-risk neuroblastoma after bone-marrow transplantation in *13-cis-retinoic acid*-sensitive cells. The treatment shows a lower expression of PBX1 in primary NBL tumour tissue and is indicative of the therapeutic activity. [26] In 1994, Matthay et al. concluded in a study that high-risk non-progressive neuroblastoma can be treated with a series of intensive multimodal therapy followed by isotretinoin maintenance therapy. Isotretinoin is capable of decreasing proliferation and in vitro induction of differentiation in neuroblastoma cell lines. However, since it was not that efficient, FDA restricted its approval for a very long period. Recently Isotretinoin therapy passed the FDA approval for treatment of pediatric and adolescent neuroblastoma because of its combination with immunotherapy, anti-GD2 antibody dinutuximab and cytokines. [27]

In a randomized placebo-controlled study it was seen that Isotretinoin was used as an additional therapy in squamous-cell carcinoma of the head and neck.[28] It is also highly beneficial in treating Keratocanthoma in oral doses while only marginal results were seen in the treatment of Myelodysplastic syndromes.[29] However, a randomized Phase III Trial of Low-dose Isotretinoin showed that Isotretinoin does not significantly reduce second primary tumours, as statistically, the results were very depressing and could not show effective results.[30] High doses of Isotretinoin such as 1-2mg/kg/day is highly effective for the treatment of leukoplakia but the toxicity in the regimen results in worsened situations and fatalities. A low dose of Isotretinoin has a high therapeutic index in the case of oral premalignant lesions. [31]

A SKICAP-BCC/SCC study was conducted between 1985 and 1990 to identify the role of isotretinoin in the treatment of non-melanoma skin cancer (NMSC) in which doses ranged between 0.2-0.8mg/kg/day. It was concluded in the study that Isotretinoin is involved in the treatment of basal cell carcinoma (BCC) in the dose of 0.2-8.2mg/kg/day within two months to a year. However, treatment of squamous cell carcinoma (SCC) with Isotretinoin in the dose of 0.5-3mg/kg/day showed similar results within two weeks of administration. A dose as high as 5-10mg of Isotretinoin was proved to be ineffective in treating NMSC rather it causes toxicity that affects the mucocutaneous region severely.[25][32]

A randomized phase-III clinical trial conducted in the early 2000s showed the difference between active smokers and people who quit smoking based on bronchial metaplasia when treated with Isotretinoin. Active smokers had worse metaplasia when compared with the people in the placebo group or study population who were not actively smoking. The interaction between smoking and Isotretinoin administration is highly beneficial in forming the basis of chemotherapeutic activities which is still under primitive research and needs more evidence to move ahead. [33] Continued treatment with Isotretinoin was concluded to be harmful in current smokers while it was considered safe in non-smoker and former smokers with an extended followup. Alternatively, another study suggested resistance to Isotretinoin in non–small cell lung cancer patients due to the expression of retinoic acid receptors due to the suppression of retinoic acid receptor β2 expression in smokers by tobacco carcinogens or nicotine which eventually fails to prevent second primary tumors.[30][34]

ADVERSE EFFECTS OF ISOTRETINOIN

Adverse effect on the lipid profile

Isotretinoin, like the other retinoids, is known to affect serum lipid levels. It also affects cholesterol and low-density lipoprotein levels, which increase in approximately 30% of patients. Isotretinoin has been known to cause increased serum levels of liver enzymes in approximately 15% to 20% of patients. These levels usually normalize within a few weeks despite the continuation of the medication and are usually insignificant. It is rare to develop changes in liver function if it has not presented within the first two months. [35][36] According to Charakida et al, approximately 15% of patients treated with isotretinoin show mild to moderate elevation of liver function tests especially bilirubin, alkaline phosphatase, and liver enzymes. Various preclinical studies show that *13-cis- retinoic acid*has an adverse effect on lipid profile. [37]

Gustafson *et al.,* in the year 1990 had studied the metabolism of very-low-density lipoproteins in rats at a dose of 10mg/day for eleven days. This study showed a change in lipoprotein concentration like increased VLDL triacylglycerol levels. The plasma triacylglycerol levels increased within the first few days after isotretinoin treatment, and there was no effect on total plasma cholesterol, plasma HDL2 cholesterol, or plasma combined LDL and HDL1 cholesterol. The study concluded that hypertriglyceridemia seen after isotretinoin treatment is associated with reduced VLDL uptake by parenchymal cells of the liver. [38]

Okan Kijilyel et al. carried out a retrospective study with 322 acne patients who took isotretinoin from June 2009 to June 2012. This study was done to determine the effects of oral Isotretinoin on lipids and liver enzymes in Acne Patients. All patients had received oral isotretinoin 0.5 to 1 mg/kg daily. The majority of patients received 30 to 40 mg daily. Patient medical records included age, gender, white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin count, and level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), Triglycerides (TG), Low-Density Lipoprotein (LDL), and High-Density Lipoprotein (HDL) at the beginning of treatment. AST, ALT, TG, LDL, and HDL levels also were measured at 3- and 6-month follow-up. It was noticed that there were statistically significant increases in TG and LDL levels($p<0.001$) while HDL levels were shown to decrease ($p=0.016$). There was also a statistically significant increase in AST levels ($p=0.72$), but there was no statistical significant increase in ALT levels. Thus, it was concluded that isotretinoin appeared to have a more substantial effect on lipids than liver enzymes.[39]

Teratogenic effect of Isotretinoin

The most concerning side effects of isotretinoin are teratogenicity and an increase in the rate of spontaneous abortion. Craniofacial abnormalities include ear defects, dysmorphism, cleft palate, depressed nasal bridge, and hypertelorism. Berard et al., in their research article entitled *Isotretinoin, pregnancies, abortions and birth defects: a population-based prospective,* analyzed the population-based pregnancy rates, elective and accidental abortions, and teratogenic effects associated with the use of isotretinoin. Patient databases from the period of 1984-2002 were studied. The databases were collected using the RAMQ (medical and pharmaceutical data), MED-ECHO (hospitalizations), and IQS (births and deaths) databases. It was concluded that incidence rates of pregnancy while on isotretinoin are four times greater than what has been reported in the literature thus far, and there were higher elective abortion rates. [40] A. Malvasi et al., in their review article regarding the teratogenic effect in pregnancy, presented a short report of a 32-year old healthy pregnant woman who underwent abortion and gave birth to thoraco-omphalopagus conjoined twins because of malformed pregnancy. Checking into the clinical history, reveled that the patient was on isotretinoin for seven months and got pregnant after three months of stopping the medicament. Ultrasonography showed the malformed pregnancy, and with the request of the patient to interrupt gestation, abortive delivery was carried out. So, this shows how isotretinoin can cause teratogenic effects in females who are pregnant. [41]

Psychiatric effect of Isotretinoin

Isotretinoin has multiple dose-dependent side effects related to psychological and gastrointestinal disorders. Isotretinoin has been associated with a rising number of recorded cases of psychological side-effects such as depression, suicide, violence, paranoia, mood fluctuations, aggressive behavior, anger, bipolar disorder, schizophrenia, and obsessive-compulsive disorder during post-market safety monitoring. Goodman has put forward three lines of evidence to associate Retinoids with schizophrenia. Firstly, the symptoms related to retinoid toxicity resemble the stigmata of schizophrenia, i.e., thought, disorder, mental deficit, enlarged ventricles, microcephaly, and congenital malformations. Secondly, there is a homology between the loci linked to schizophrenia. Finally, it has been studied that the transcriptional activation of the dopamine (D2) receptor and the genes responsible for schizophrenia are monitored by retinoic acid. [37]

Alan Byrne et al. reviewed case histories of patients who had received treatment with isotretinoin and had suffered from depression-related symptoms. The first case cited in the article

was about a 28-year-old woman who had low mood agitation and features of depression. She was found to have disturbed sleep, decreased appetite, reduced concentration, increasing levels of irritability without apparent cause. Her Hamilton Rating Scale score was 26. Checking the patient's history, it was found that the patient had been four months of treatment with isotretinoin for cystic acne and all the depression side effects started during treatment. To treat the patient, she was given a course of imipramine, and there was a gradual improvement in her mood and her ability to function in social situations. Further, she secured a rating of 9 on the Hamilton Rating Scale. The second case was about an 18-year-old man who wanted to commit suicide by taking an overdose of Tazadone tablets. The patient had a deteriorating mood, loss of interest, apathy, insomnia, anergia, and anhedonia, and marked irritability. The patient scored 31 on the Hamilton Depression Scale. The patient, when admitted, was receiving isotretinoin therapy for cystic acne for more than five months. To treat the patient, the doctors provided fluoxetine therapy and stopped retinoid therapy, and there was a gradual improvement in the mood over the next four weeks. The third case was a 20-year-old woman referred for assessment of depression, fearfulness, and suicidal ideation, which had been present for several weeks. The patient scored 29 on the Hamilton Depression Scale. The clinical history showed that the patient was receiving isotretinoin therapy for an acne condition intermittent during the previous year and was continuing due to a good dermatological response. Thus, the doctors prescribed fluoxetine therapy, and the patient's mood improved considerably, and she was discharged after two weeks. [42]

Mucocutaneous effect of Isotretinoin

Mucocutaneous side effects related to isotretinoin use that is observed from the first week of treatment includes chelitis, nasal dryness and dermatitis. Chelitis is observed in greater than 90% of patients and is dose-dependent. Dermatitis is commonly seen in the forearms and hands and is more prevalent in the winter months. Less than 50% of patients treated with isotretinoin will experience clinically notable xerosis which is often associated with significant pruritus. Asthma exacerbation has also been seen in isotretinoin treated patients and has been related to dryness of pulmonary mucosa. [37] According to Ellis CN et al, the other types of mucocutaneous effects include diffuse alopecia and increased nail brittleness and, in most cases, resolving within 2 months after ceasing treatment. Dermabrasion and waxing are mainly prevented during isotretinoin treatment. [43]

OTHER SIDE EFFECTS OF ISOTRETINOIN

Apart from the above side effects, isotretinoin is also found to cause ocular side effects, bone and muscle defects, hematologic effects, GI Effects but minimal. Brelsford et al., in their review article, have mentioned gastrointestinal effects reported to cause by isotretinoin therapy. Patients with known ulcerative colitis have been treated successfully with isotretinoin, and if at all the patient develops gastrointestinal symptoms, the medication should be stopped, and evaluation should be started. Isotretinoin has been reported to cause nausea, diarrhea, and abdominal pain, but this is uncommon. Hematologic effects like thrombocytopenia and neutropenia have been reported as complications of treatment, but they are rare. [44]

Fraunfelder et al., in their article, have mentioned several ocular side effects related to isotretinoin therapy and the most commonly reported is sicca(dry eyes), which can be connected to both atrophies of the meibominal glands and changes in the tear film. Secondary ocular side effects include keratitis, blepharoconjunctivitis, poor tolerance of contact lenses, and photophobia.[45] Maclean H et al. and Halpagi P et al. have mentioned that the most common ocular side effects are the loss of dark adaptation and loss of color vision. Most of these cases are reversible as the effects get cure on cessation of the medication.[46][47] The mechanism for the loss of night vision is related to the inhibition of ocular retinal dehydrogenases, which decreases the amount of visual chromophore 11-*cis*-retinal. [48]

Clinical Trials on Isotretinoin to determine its therapeutic use other than treating acne and oral leukoplakia

We carried out data mining of completed clinical trials from clinicaltrials.gov on Isotretinoin therapy, the results of which have been

Study Title, clinicaltrails.gov Trial ID	Primary Outcome measure of the study	Study Result
Determining the Effect of Low-dose Isotretinoin on Proliferative Vitreoretinopathy (PVR) **Trial Id: NCT01445028** [50]	**Study Design:** Non-Randomized, Parallel, and Open Label study **Phase:** Phase 4 **Disease under study:** Vitreoretinopathy	
	Evaluation of Retinal Attachment Rate (single surgery anatomical success rate) of study subjects after 12-week course of isotretinoin 20 mg.	The single surgery anatomic success rate was higher in subjects exposed to isotretinoin versus historical controls. Thus, oral isotretinoin may reduce the risk of PVR-associated recurrent retinal detachment in eyes with primary RRD at high risk of developing PVR.
A Pilot Trial of *13-cis- retinoic acid*(Isotretinoin) for the Treatment of Men With Oligoasthenoteratozoospermia **Trial Id: NCT02061384** [51]	**Study Design:** Non-Randomized, Parallel, and Open Label study **Phase:** Phase 2 **Disease under study:** Oligoasthenoteratozoosp-ermia	
	The primary outcome of the study was to measure the Millions of sperm per ejaculate in men treated with *13-cis-retinoic acid*.	The study found significant subset of men with Oligoasthenoteratozoospermia had increased sperm output when treated with isotretinoin. (p=0.0006)
Feasibility/Phase II Study of hu14.18-IL2 Immunocytokine + GM-CSF and Isotretinoin in Patients With Relapsed or Refractory Neuroblastoma **Trial Id: NCT01334515** [52]	**Study Design:** Non-Randomized, Parallel, and Open Label study **Phase:** Phase 2 **Disease under study:** Recurrent Neuroblastoma	
	The primary outcome of the study was to evaluate the number of Patients With Unacceptable Dose Limiting Toxicities (DLTs)	The study concluded that hu14.18-IL2 given with GM-CSF and isotretinoin is safe and tolerable in Patients With Relapsed or Refractory Neuroblastoma
Interferon Alpha (NSC# 377523) Plus *13-cis- retinoic acid*Modulation Of BCL-2 Plus Paclitaxel For Recurrent Small Cell Lung Cancer **Trial Id: NCT00062010** [53]	**Study Design:** Interventional and Open Label study **Phase:** Phase 2 **Disease under study:** Lung Cancer	
	Assess the response of treated participants in each response category by RE*CIS*T criteria every 6 weeks	The study concluded that the addition of Isotretinoin and interferon alpha to paclitaxel did not improve outcomes for recurrent SCLC.
A Randomized Phase II Trial of Concurrent Temozolomide and Radiotherapy Followed by Dose Dense Versus Metronomic Temozolomide and Maintenance *Cis*-Retinoic Acid for Patients With Newly Diagnosed Glioblastoma and Other Malignant Gliomas **Trial Id: NCT00200161** [54]	**Study Design:** Randomized, Parallel, and Open Label study **Phase:** Phase 2 **Disease under study:** Glioblastoma	
	12 Month Overall Survival of Patients With Newly Diagnosed Glioblastoma Multiforme Treated With Concurrent Temozolomide and Radiotherapy Followed by Dose Dense or Metronomic Dosing of Temozolomide and Maintenance *Cis*-retinoic Acid.	The dose-dense and regimens of metronomic temozolomide were well-tolerated interventions. Toxicity was modest. The dose-dense regimen showed good, 1-year survival of 80%.

Table 2: Completed Clinical Trials on Diseases Conditions other than Leukoplakia and Acne.

published in open access journals (**Table II**). This data mining was done to find disease conditions other than acne and oral leukoplakia, for which Isotretinoin has gone through clinical trials.

CONCLUDING REMARKS

Isotretinoin is a drug that is commonly used to treat nodulocystic acne. It is a very well-tolerated drug, aside from its side effects. Various management procedures have been recommended to minimize the side effects caused by therapy with isotretinoin. Different interventions have been in development to mitigate teratogenicity, and the most accepted of which is the iPLEDGE Programme. The iPLEDGE Programme requires the physician to enter a negative pregnancy result into the computer system before the pharma*cis*t can dispense isotretinoin. When using isotretinoin, micro-dried progesterone (mini-pill) as a method of birth control should be avoided. Many physicians have suggested that at least two negative pregnancy tests responsive to 25 mlU/ml should be done before beginning therapy with isotretinoin. The pregnancy tests should have a gap of 30 days. A serum test from a certified laboratory is necessary. It is advised to carry out effective contraceptive methods and avoid getting pregnant until at least one month after cessation of therapy.[26][55] History screening profiles like night-blindness, use of contact lenses, and sicca should be observed in patients before taking isotretinoin.[27] The claim that oral isotretinoin is extremely successful in treating acne vulgaris is confirmed by numerous clinical trials, observational database reviews, comprehensive global expertise, and the consensus view of multiple consultants who have assisted in the development of acne treatment guidelines.[28] Hence if proper screening and preventive measures are carried out then isotretinoin remains a useful medication for the treatment of acne vulgaris. Recent clinical trials on Isotretinoin has shown promising results o using the drug for many other diseases. Isotretinoin is thus a therapeutic drug which requires more clinical trials and extensive research to treat many other life-threatening diseases in the future.

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- **Wrote Section 1, Section 2, Scetion 3, Scetion 6, and Section 7 of the paper:** Priyabrata Panda
- **Wrote Section 4 of the paper:** Priyabrata Panda, Mohammad Sahil
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