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Safety and side effects of the acne drug, oral isotretinoin

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Isotretinoin is a very effective medication for the treatment of severe recalcitrant acne. However, its use is associated with many side effects, some of which can be very serious. The most important issue is its teratogenicity, which has resulted in new pregnancy prevention policies and programmes implemented by the manufacturer. Recently, the association of isotretinoin with depression has been recognised and new guidelines have been adopted for this possible side effect. The most common adverse events, observed during treatment, are mucocutaneous and ophthalmological. In addition, laboratory abnormalities and effects in the nervous, musculoskeletal, gastrointestinal, pulmonary and other systems have been described.

Keywords: depression, isotretinoin, mucocutaneous side effects, side effects, teratogenicity

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1. Introduction

Isotretinoin, or 13-*cis* retinoic acid, is a vitamin A derivative that was initially introduced in the US in 1982 for the treatment of nodulocystic acne. Its introduction was a landmark, revealing new therapeutic options in the treatment of acne. It is the only medication that affects all of the major aetiological factors implicated in acne. Acting on keratinocytes, it normalises their maturation and adhesion and, as a result, it reduces comedone formation [1]. It decreases sebocyte-mediated androgen synthesis [2] and significantly reduces sebum excretion within a month of initiating therapy [3]. It also reduces the numbers of *Propionibacterium acnes* and Gram-negative *bacilli* on the skin [4] and directly reduces neutrophil chemotaxis [5,6].

2. Efficacy

Isotretinoin is a very effective acne treatment. It has been shown to be superior to erythromycin [7] and to the combination of oral tetracycline and topical retinoic acid [8]. The overall response rate of isotretinoin is 84.22 – 86.71% [9]. However, relapses can occur at any time after discontinuation of the treatment. The relapse rate varies. It is usually low, ~ 21% [9,10], although there are reports with much higher relapse rates of ~ 40 – 60% [11-14]. The relapses are dose-dependent and are lower if a cumulative dose of 120 mg/kg is achieved. Age and severity of acne can predict relapses [9,10].

3. Side effects

Although isotretinoin is a very effective drug, its clinical use has always been associated with reports of adverse events with various implications for the patients. It is therefore essential that physicians are aware of the side effects that may occur during isotretinoin therapy.

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3.1 Teratogenicity

The most serious adverse event associated with isotretinoin use is teratogenicity. Although vitamin A congeners have been well-established as teratogenic in animal models since the 1960s, humans were found to be more susceptible to the teratogenic effects of isotretinoin compared to rats and mice [15]. The available data indicate that exposure to 0.4 – 1.5 mg/kg/day of isotretinoin during the first weeks of pregnancy causes miscarriage in 22% of cases and congenital malformations in 18% [16]. However, the relationship between the time of exposure and the defects observed remains unclear. As a result, exposure to isotretinoin at any time during pregnancy is considered hazardous.

The malformations observed are characteristic for isotretinoin and comprise the retinoic acid embryopathy [17]. The pattern of defects includes cardiovascular abnormalities, CNS abnormalities, craniofacial defects and thymus gland abnormalities [18], as shown in Table 1.

Furthermore, developmental problems, including sensory, motor and cognitive defects, have been reported in 50% of isotretinoin-exposed, apparently healthy children. These problems include deafness, blindness, learning disabilities and poor hand–eye coordination. Limb reductions and duplications have also been described [15].

There are three possible mechanisms implicated in the embryonic malformations observed during isotretinoin therapy: inhibition of cellular migration from the neural crest; alteration of the apoptotic patterns in the visceral arches during development; and other undetermined alterations in gene transcription mediated by retinoic acid receptors (RARs) [15].

To prevent the teratogenic effects of isotretinoin, a pregnancy prevention programme (PPP) was implemented in 1988 in accordance with FDA recommendations. In the context of this programme, educational materials for physicians and patients and reimbursement to women for contraceptive counselling by a physician were offered [19].

Although the outcomes of the PPP were encouraging, exposed pregnancies continued to occur. As a result, in 2001, the FDA introduced the System to Manage Accutane® Related Teratogenicity (SMART) programme [20].

3.1.1 UK guidelines for isotretinoin-induced teratogenicity

The guidelines from the British Association of Dermatologists suggest that every action should be taken to ensure that the risks of teratogenicity are fully understood by all female patients being considered for isotretinoin treatment. It is therefore suggested that all female patients of childbearing age should have a pregnancy test, preferably performed on blood, within 2 weeks of initiation of the treatment, and that treatment should begin on day 3 of the patient's next menstrual cycle following a negative pregnancy test. The patient should also use appropriate contraception for 1 month before starting treatment and continue to do so for at least 1 month after cessation of the treatment. Ideally,

contraception should be hormonal. The combined contraceptive pill and injectable or implantable hormonal therapy are recommended, whereas the progesterone-only pill may be less reliable to those taking isotretinoin.

In the US, the SMART programme represents a more stringent birth control policy. It includes the simultaneous use of two reliable forms of contraception throughout treatment and two negative pregnancy tests before initiation of therapy. The second pregnancy test must be performed in the first 5 days of the woman's menstrual period immediately preceding isotretinoin therapy or 11 days after the last act of unprotected intercourse in cases of amenorrhoea. In addition, no more than a 30-day supply should be prescribed at each visit and women should have a negative pregnancy test prior to receiving their prescription [15].

3.2 Mucocutaneous side effects

3.2.1 Cheilitis and nasal dryness

Mucocutaneous toxicity is the most commonly observed side effect of isotretinoin use with a very early onset, even from the first week of treatment. The most bothersome of the mucocutaneous manifestations is cheilitis. It is observed in > 90% of patients within days of introducing therapy and is dose-dependent [15,17]. Severe forms of erosive and exfoliative cheilitis have also been described and clinical discomfort and deterioration of aesthetic appearance may cause severe stigmatisation. To alleviate cheilitis, lip salves should be regularly applied and lip licking should be avoided, since it substantially aggravates cheilitis. Apart from cheilitis, dryness of nasal mucosa may also be observed. Nosebleeds are the apparent manifestations of this dryness. The epistaxes are usually mild and self-limiting, requiring no packing or cautery. Lubrication to the anterior nares may reduce the dryness of nasal mucosa [21].

3.2.2 Dermatitis

Another manifestation of isotretinoin therapy is dermatitis. The neck and face can be involved, and, in this case, facial dermatitis should be differentiated from facial erythema, which is commonly seen with oral isotretinoin therapy. Dermatitis is commonly seen on the forearms and hands and is more prevalent in the winter months and in low humidity situations [22]. It may present either as primary irritant dermatitis, discoid eczema, eczema craquele, nummular eczema, follicular eczema, or acute pityriasis rosea [23–26]. Less than 50% of patients treated with isotretinoin will experience clinically significant xerosis, which is often associated with significant pruritus. This occurs more often in patients with an atopic history [27]. Occasionally, desquamation occurs with accentuated peeling of the palms and soles. However, this is more common with acitretin therapy for psoriasis than with isotretinoin treatment [17]. Asthma exacerbation has also been seen in isotretinoin-treated patients and has been related to dryness of the pulmonary mucosa [28,29].

Diplopia, optic neuritis and eyelid oedema without significant eyelid irritation have also been reported. Finally, subconjunctival haemorrhage should be included in the list of possible reactions. Although potentially alarming, it is usually asymptomatic and self-limiting, requiring no treatment [61].

Most of these ophthalmological symptoms can be managed with artificial tears and avoidance of contact lenses during the period of treatment. In some cases, topical ophthalmological antibiotics may be needed and special attention should be directed towards those reporting symptoms of a severe nature [15].

3.5 Psychiatric effects

There have been serious concerns about the possible association between isotretinoin therapy and depressive symptoms. Since 1983, there have been a number of case reports as well as small case studies to support this relationship. In 1996, two cases of suicide related to isotretinoin treatment were described. In February 1998, this complication was added to the side effects of the medication [62]. To establish causality, depressive symptoms must develop soon after the initiation of treatment with isotretinoin, resolve after drug discontinuation, and recur following drug rechallenge.

Various data concerning depression as an adverse effect of isotretinoin are available. Between June 1982 and May 2000, the FDA received reports of 431 cases of depression, suicidal ideation, suicide attempts and completed suicide in US patients on isotretinoin therapy. In 22% of these cases, a history of psychiatric illness was also reported, and in 57%, co-morbid factors were identified [63]. Furthermore, isotretinoin is classified in the fourth, fifth and tenth place in the FDA's database based on the number of reports for depression, serious depression and suicide attempts, respectively [64]. Isotretinoin is also the only non-psychotropic medication in the ten highest-ranking drugs for suicide attempts [65].

In addition to the FDA database, a MEDLINE search (January 1966 – May 2003) found 29 reported cases linking isotretinoin to depression and suicide, amongst which there were two cases with positive dechallenge/rechallenge of isotretinoin. The onset of mood alteration was variable and the depression was unrelated to the dosage, duration of treatment or prior exposure to isotretinoin. Resolution of symptoms was usually rapid, within 2 – 7 days, after discontinuation of therapy. In the majority of cases, depression was thought to be an idiosyncratic adverse effect of isotretinoin therapy [62]. Along the same lines, Jick *et al.* failed to show an association between depression, suicide or other psychiatric disorders and isotretinoin in a large cohort of acne patients. In this study, isotretinoin was compared to oral antibiotic regimens [66].

Moreover, in presentations to the FDA, Hoffmann-La Roche reviewed all cases of psychiatric adverse events received worldwide by Roche Global Drug Safety between 1982 and April 1999. There were 1247 cases of mood disorders. Among these, 367 cases had positive dechallenge and 23 had positive dechallenge/rechallenge. In this report, the overall rates of

depression and suicide in patients on isotretinoin were far below the baseline rate of the general population. This suggests that these symptoms were unrelated to the use of the drug [62].

On the other hand, there is evidence to support decreased levels of anxiety and depression in patients on isotretinoin. Not surprisingly, this beneficial effect was noted mostly in patients with the greatest clinical improvement [67-70]. Whilst these studies demonstrate that mood improves as acne improves, causality cannot be established in these cross-sectional studies.

3.5.1 Mechanistic approaches of isotretinoin-related psychiatric effects

Vitamin A and its metabolites cross into the CNS and their receptors are found in the brain. In this way, they may interact in neuronal pathways, such as dopamine signalling, which are known to be involved in mood and cognitive disorders [71].

In addition, vitamin A plays a significant role in gene regulation and expression in brain neurodevelopment. Goodman was the first to associate dysregulation of this action of retinoids with schizophrenia [72]. Schizophrenia is now considered to be a neurodevelopmental disorder, with the first evidence of the disorder occurring in the mid-gestational period, when fetal brain activity is still developing. Goodman has put forward three lines of evidence to establish this association. First, symptoms related to retinoid toxicity share resemblance with the stigmata of schizophrenia (i.e., thought disorder, mental deficit, enlarged ventricles, microcephaly, congenital malformations). Second, there is homology between the loci linked to schizophrenia and the loci of genes within the retinoid system. Finally, it is well known that the transcriptional activation of the dopamine D2 receptor and numerous schizophrenia candidate genes are regulated by retinoic acid [72].

3.5.2 UK guidelines for isotretinoin-induced depression

Since it is not feasible to predict the occurrence of depression in isotretinoin-treated acne patients, the British Association of Dermatologists (BAD) recommends that:

- A direct enquiry about previous psychiatric health should be performed in all patients who are being considered for isotretinoin treatment.
- All patients and the parents of adolescent patients should be aware of these side effects. Records of any mood change in a realistic, non-judgemental way should be kept and family members and friends must be advised to report if any such change occurs.
- Direct enquiry about psychological symptoms should be made at each clinic visit.
- If symptoms of depression or mood change do occur, then ideally, isotretinoin should be discontinued. However, this decision relies on the patient, who may wish to continue with the drug because of the benefit to their skin. In this case, specialist psychiatric support should be obtained.
- If serious psychiatric illness is suspected, there should be an immediate referral to a psychiatrist.

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In the US, in addition to the BAD guidelines, a psychiatric consent form and yellow label prescriptions are required. Moreover, in the FDA guidelines, patients are suggested to stop treatment if any of the following occur [201]:

- Start to feel sad or have crying spells.
- Lose interest in activities they once enjoyed.
- Sleep too much or have trouble sleeping.
- Become more irritable, angry or aggressive than usual (for example, temper outbursts, thoughts of violence).
- Have a change in appetite or body weight.
- Have trouble concentrating.
- Withdraw from friends or family.
- Feel like they have no energy.
- Have feelings of worthlessness or inappropriate guilt.
- Start having thoughts about hurting themselves or taking their own life (suicidal thoughts).

3.6 Neurological effects

Neurological reactions have been reported to occur with isotretinoin use. Fatigue is common, is usually transient and occurs during the initiation of the treatment. Headaches occur with a frequency of ~ 16% and they do not usually require any treatment. Other neurological symptoms include lethargy, dizziness, drowsiness, insomnia, malaise, nervousness, seizures, confusion, paresthesias, stroke, syncope, weakness, optic disk oedema and pseudotumour cerebri (PTC) [15,73-78].

Benign intracranial hypertension, or PTC, was first described by Gerber *et al.* [79] in 1954 and has long been associated with vitamin A administration. PTC is accompanied by symptoms such as papilloedema, vision problems, nausea and severe headaches. PTC occurs in 30 – 50% of patients with hypervitaminosis A and is characterised clinically by three criteria: neurological and ocular symptoms and signs of increased intracranial pressure, which may include headache, nausea, transient visual obscurations, sixth-nerve palsies and papilloedema; radiologically demonstrable normal or small-sized cerebral ventricles; and elevated cerebrospinal fluid. PTC has been associated with isotretinoin therapy and the risk of PTC may increase in combination with tetracycline [76].

Finally, tinnitus and hearing problems have been noted. Tinnitus is rare, dose-dependent and reversible, whilst the hearing impairment may persist after discontinuation of the treatment [21].

3.7 Gastrointestinal effects

Nonspecific gastrointestinal (GI) symptoms (such as nausea, diarrhoea and abdominal pain) have been reported with isotretinoin therapy. There are also conflicting reports regarding the possibility of isotretinoin therapy causing or exacerbating the symptoms of inflammatory disease [80]. Isotretinoin has been administered on multiple occasions to patients with known ulcerative colitis and Crohn's disease with no complications arising. Rectal biopsy specimens from patients with inflammatory bowel disease and from normal control

subjects undergoing isotretinoin therapy do not demonstrate any changes in the number or the morphology of goblet cells. On the other hand, there are reports of inflammatory flares during isotretinoin therapy and, in these cases, discontinuation of the drug is indicated [81-83]. Other GI adverse effects reported with isotretinoin therapy include pancreatitis, due to hypertriglyceridaemia, clinical hepatitis [201], appendicitis, bleeding and inflammation of the gums, oesophagitis, colitis, ileitis and proctosigmoiditis. These side effects are largely reversible when the drug is discontinued [84-86].

3.8 Rheumatic/vascular effects

Arthralgia is very common in patients treated with isotretinoin, and cases of lower back pain and costochondral chest pain have been noted [22,87]. A few cases of acute, aseptic arthritis marked by elevated antinuclear antibodies [88,89], and a case of adult-onset Still's disease [90], have been reported during isotretinoin therapy. Acute arthritis appears to be reversible, but in some cases the pain may persist for years after cessation of the treatment [91,92].

Necrotising and polyarteritis-like vasculitis and allergic vasculitis with purpura involving extracutaneous areas (including renal) and extremities have also been reported [93-96].

3.9 Pulmonary effects

Respiratory side effects related to isotretinoin are rare. These include bronchospasm, asthma exacerbation, eosinophilic pleural effusions, respiratory infections and voice alterations [97,28]. These symptoms usually resolve when treatment is discontinued.

3.10 Renal/urinary effects

Renal side effects related to isotretinoin therapy are quite rare. These include glomerulonephritis, urethritis, proteinuria and one case of nephrotic syndrome. In most cases, serum creatinine levels return to normal and proteinuria disappears after discontinuation of treatment [98-100].

3.11 Genital effects

Isotretinoin may affect the menstrual cycle but there are no data to suggest that these effects are permanent or result in decreased fertility [101,102].

As far as men are concerned, spontaneous abortion or teratogenicity induced by paternal isotretinoin therapy have not been reported. The effect of retinoids on androgen levels and spermatogenesis has been studied in animals and humans. No changes were noted in serum testosterone levels but there was a significant decrease in 5- α -dihydrotestosterone, 5- α -androstane-3- α , 17- β -diol glucosiduronate and androsterone glucosiduronate levels following treatment [103,104]. It is unlikely that short courses of isotretinoin treatment have a significant or long-lasting effect on spermatogenesis or fertility. However, the effect of the chronic use of isotretinoin on spermatogenesis has urged some investigators to be cautious, due to the decreased spermatogenesis observed in gerbils [105].

3.12 Laboratory abnormalities

In addition to the previous side effects, the impact of isotretinoin on liver function and lipid metabolism is a source of concern.

Approximately 15% of patients treated with isotretinoin show mild-to-moderate elevation of liver function tests (LFTs) (especially bilirubin, alkaline phosphatase and liver enzymes). Although hepatotoxicity is a fairly rare event, several cases of clinical hepatitis possibly or probably related to isotretinoin therapy have been noted and the potential for liver problems during isotretinoin therapy exists [106].

It seems that the more important and frequent laboratory side effect of retinoid administration concerns lipid metabolism. Reversible hypertriglyceridaemia has been reported to develop in 25% of patients on isotretinoin, usually mild-to-moderate (2.3 – 6.9 mmol/l), within the first month of therapy [107]. A concomitant increase in total cholesterol and low-density lipoprotein (LDL) cholesterol levels by ~ 15% compared with pretreatment levels and a decrease in high-density lipoprotein (HDL) concentrations, are also frequently observed in these patients. Whilst the onset of hypertriglyceridaemia appears unpredictable, the elevation of cholesterol levels is primarily observed in patients with pre-existing hyperlipidaemia or obesity, especially android obesity [21]. The mechanism of these changes has not been established. However, hypertriglyceridaemia is shown to be due, at least in part, to the retinoid X receptor-mediated increase in expression of a molecule known as apo C-III that acts as an antagonist of plasma triglyceride catabolism [15]. As far as the mechanism of hyperlipidaemia is concerned, it is suggested that retinoids directly influence both HDL production and catabolism and they can also affect HDL metabolism indirectly by their effects on triglyceride concentrations [107].

It has been speculated that this elevation of serum lipid levels may lead to an increased risk for cardiovascular disease. However, the significant variations of serum lipid and lipoprotein levels do not influence the overall risk for atherosclerosis in young and healthy patients on short courses of isotretinoin therapy [108]. In addition, acute pancreatitis can rarely occur in cases of severe hypertriglyceridaemia [109,110].

After discontinuing isotretinoin therapy, serum LFTs and lipid levels usually return to baseline parameters within a few months. The evidence so far suggests that blood tests should be performed prior to the onset of therapy and repeated after 1 and 2 months of therapy. Dose reduction and/or the addition of antihyperlipidaemic agents is warranted if very high levels of triglycerides (> 500 mg/dl) occur and dose reduction should be considered when LFTs are 2- to 3-fold higher than normal values. If there is no response to these measures, discontinuation of therapy is required [111,112].

Other reversible and dose-dependent changes in laboratory variables include a decrease in white blood cell and neutrophil counts, thrombocytopenia, agranulocytosis,

elevated erythrocyte sedimentation rate (ESR) and increased homocysteine and uric acid levels [113,114]. Rarely, especially in patients with underlying haematological disease, increased bleeding times may be seen. Isotretinoin can also reduce insulin sensitivity and cause changes in blood glucose levels, predominantly in diabetics [115].

4. Conclusion

Over recent years, isotretinoin has proven its effectiveness in the treatment of severe recalcitrant acne. Nevertheless, it is associated with a long list of side effects that are frequent, varied and, at times, severe. The most important side effect is its teratogenicity, which has resulted in new pregnancy prevention policies and programmes implemented by the manufacturer. A relatively new concern is that of mood changes and depression associated with isotretinoin use. Although no causal link has yet been established between isotretinoin and depression, dermatologists should be aware of this possible serious side effect, and if such symptoms occur, isotretinoin treatment should be discontinued and if necessary specialist psychiatric support should be obtained.

The most common adverse reactions that occur in almost all patients on isotretinoin therapy are those involving the skin and mucus membranes. In addition, side effects affecting almost all systems have been reported. These reactions may vary from mild to severe and are usually reversible after discontinuation of the treatment. However, they can sometimes persist and can cause severe distress to the patient.

5. Expert opinion

Isotretinoin is a highly effective acne drug but with very significant side effects. It can be an excellent and effective therapeutic option for acne as long as it is used with caution. It should be administered in cases of severe acne or acne unresponsive to conventional oral and topical therapies. Acute flares of acne are often encountered, particularly when very inflammatory acne is being treated. In the authors' experience, combination of an antibiotic with isotretinoin for the first 4 weeks of treatment will prevent this flare. Tetracyclines should be avoided at this stage due to the increased risk of benign intracranial hypertension. Isotretinoin should be administered at a dose of 1 mg/kg daily and it should be continued until the patient is totally clear of acne lesions. In some patients with very inflammatory acne where the possibility of an acute flare on starting isotretinoin is high, a lower starting dose at 0.5 mg/kg/day should be used for the first 6 weeks and then increased to full dosage. Regardless of the exact regimen, a cumulative dose of 120 mg/kg should be given to reduce the chance of relapse after isotretinoin therapy. Patients should be informed of all the possible side effects, and if these should occur, they should be addressed accordingly.