1.1. Isotretinoin and erectile dysfunction

Introduction

Isotretinoin (Roaccutane®) is a retinoid compound and a stereoisomere of all-trans retinoic acid (tretinoin). Isotretinoin is indicated for the systemic treatment of *severe types of acne* (such as nodular or conglobate acne, or acne that is at risk of causing permanent scarring) resistant to adequate courses of standard therapy with systemic anti-bacterials and topical therapy [1]. Isotretinoin has been granted marketing authorisation in EU Member States (apart from Sweden and Norway where the product is sold on special licence) since 1983. Like all retinoids, isotretinoin is teratogen and is contraindicated during pregnancy to avoid congenital defects. Isotretinoin should only be prescribed to women of childbearing potential under strict pregnancy prevention measures supported by a Pregnancy Prevention Programme [2]. The most commonly reported undesirable effects with isotretinoin are dryness of the skin and dryness of the mucosae leading to cheilitis, epistaxis and conjunctivitis [1].

Erectile dysfunction is defined as the consistent or recurrent inability to acquire or sustain an erection of sufficient rigidity and duration for sexual intercourse [3]. There are many causes of erectile dysfunction: vascular, neurologic, local penile factors, hormonal, drug induced, and psychogenic [4]. In addition to age, the best predictors of erectile dysfunction are diabetes mellitus, hypertension, obesity, dyslipidemia, cardiovascular disease, smoking, and medication use. Drugs that are known to be associated with the onset of erectile dysfunction are most antidepressants, but in particular, selective serotonin reuptake inhibitors, spironolactone, sympathetic blockers such as clonidine, guanethidine, or methyldopa, thiazide diuretics, ketoconazole and cimetidine [3].

Reports

The Netherlands Pharmacovigilance Centre Lareb received 7 reports on erectile dysfunction associated with the use of isotretinoin, in the period from 25 September 2000 until 4 December 2014. The reports are listed in Table 1.

Table 1. Reports of erectile dysfunction associated with the use of isotretinoin.

Patient, Number, Sex, Age, BMI, Source	**Drug, daily dose Indication for use**	**Concomitant Medication**	**Suspected adverse drug reaction**	**Time to onset, Action with drug, outcome**
A, 29410, M, 41-50, -, dermatologist	isotretinoin, dd50mg, acne	meloxicam, diclofenac	erectile dysfunction, epistaxis, dry lips	hours, withdrawn, unknown
B, 57946, M, 21-30, 19.8, consumer	isotretinoin, 1dd30mg, acne		erectile dysfunction, increased sweating	5 months, withdrawn, recovered

C, 62705, M, 41-50, 27.8, dermatologist	isotretinoin, dd80mg, conglobate acne	erectile dysfunction	1 month, withdrawn, recovered
D, 105226, M, 11-20, 22.6, general practitioner	isotretinoin, 2dd20mg, acne	erectile dysfunction	2 weeks, continued, not recovered
E, 107694, M, 21-30, 19.4, medical student	isotretinoin, 1dd20mg, acne vulgaris	erectile dysfunction, loss of libido, anorgasmia, somnolence, mood swings, fatigue, liver function test abnormal	6 months, continued, not recovered
F, 181294, M, 21-30, 24.0, consumer	isotretinoin, dd20mg, acne	erectile dysfunction, libido decreased	1 day, withdrawn, not recovered
G, 186328, M, 21-30, -, general practitioner	isotretinoin, 2dd 20mg, acne	erectile dysfunction, ejaculation disorder	weeks, withdrawn, not recovered

In case A the time to onset was calculated by the reported startdate of the drug and the reported startdate of the reaction, which were the same. The case was reported on the day that isotretinoin was withdrawn, which was 5 months after the initiation of the therapy. Therefore, the time to onset in this report may be incorrect.

Case B describes a patient who experienced inability to acquire and sustain an erection. The patient also reports faster and increased sweating during exercise. The report contains inconsistancy between reported latency (5 months) and calculated latency based on reported start date of the drug and reported start date of the suspect drug (9 months). The patient was recovered at the moment of reporting which was 9 days after the withdrawal of isotretinoin.

Case C describes a healthy patient who was treated with isotretinoin during a period of 2 years in the past. During this earlier treatment the patient did not experienced erectile dysfunction. The patient was recovered at the moment of reporting which was 15 days after the withdrawal of isotretinoin.

In case D was mentioned that stress could have also caused erectile dysfunction.

The past drug therapy in case E indicates that the patient experienced erectile dysfunction, mood swings, loss of libido and anorgasmia during earlier treatment with isotretinoin 4 years prior to the

reported event. The symptoms did not fully resolved after withdrawal of isotretinoin. After restart of isotretinoin the symptoms aggravated gradually.

In case F isotretinoin was withdrawn 2 months after the start. The patient has not recovered 5 years after the withdrawal of isotretinoin. Because this case was reported 5 years after the initiation of the drug and the onset of the reaction it can be assumed that the reported time to onset of 1 day may be incorrect.

In case G the patient experienced a different feeling during ejaculation. Isotretinoin was withdrawn 8 months after the start. The patient was not recovered 2 months after the withdrawal of isotretinoin.

Other factors that also might have been of influence on normal erectile functioning were pain (Case A, patient used both meloxicam and diclofenac), mood swings (Case E) and overweight (Case C).

Other sources of information

SmPC

The SmPCs of oral forms of isotretinoin available on the Dutch market do not mention erectile dysfunction or any other sexual ADR [1]. However they do mention depression (aggravated) and mood alterations. These circumstances could theoretically result in erectile dysfunction [3]. The US SPCs of isotretinoin available on the US market do not mention erectile dysfunction as a possible ADR, but they do mention abnormal menses as a possible sexual ADR [5].

Literature

During a prospective study to evaluate the efficacy and safety of isotretinoin in acne, six male patients, experienced difficulties in maintaining adequate penile erection in association with clinical symptoms of depression [6]. Coleman describes in the Lancet a case of a 29-year-old man who had problems with ejaculation during the treatment with isotretinoin. According to Coleman, Roche, the manufacturer of isotretinoin has received over 150 notifications of problems with male reproductive system, including 32 notifications of erectile dysfunction [7]. Other retinoids that have been related to the onset of erectile dysfunction are acitretin [8] and etretinate [9,10].

Databases

Table 2. Total reports of erectile dysfunction associated with isotretinoin in the databases of Lareb [11], WHO [12] and EMA [13].

Drug	Number of reports	ROR (95% CI)
isotretinoin	Lareb: 7	5.1 (2.4 – 10.8)
	WHO: 132	1.3 (1.1 – 1.6)
	Eudravigilance: 61	1.5 (1.1 – 1.9)

Prescription data

Table 3 Total number of patients using isotretinoin in the Netherlands between 2009 and and 2013 [14].

	2009	2010	2011	2012	2013
isotretinoin	17,186	18,654	17,919	18,823	19,475

Mechanism

Isotretinoin inhibits sebaceous gland function and keratinisation. The exact mechanism of action of isotretinoin has not yet been elucidated in detail, but it has been established that the improvement observed in the clinical picture of severe acne is associated with suppression of sebaceous gland activity and a histologically demonstrated reduction in the size of the sebaceous glands. Furthermore, a dermal anti-inflammatory effect of isotretinoin has been established [1].

Testosterone plays an integral role in normal male sexual function. Despite the effect of testosterone on libido is more consistent than on erectile dysfunction [15,16], testosterone deficiency can cause erectile dysfunction in both experimental animals [17] and men [3]. Sexual potency returns when testosterone levels are normalized [18]. Testosterone is necessary for maintenance of intrapenile nitric oxide synthase levels [19]. In accordance with these findings, it is plausible that decreased testosterone blood levels can be a cause of erectile dysfunction.

In an animal model it has been shown that tretinoin, a metabolite of isotretinoin, can decrease testosterone production in the testis of rats. These effects of retinoin are thought to be mediated by the activation of the retinoic acid receptor alpha in the testis [20]. In acne vulgaris patients it has been shown that treatment with isotretinoin can significantly decrease blood levels of several pituitary hormones, including testosterone [21,22]. After three months of treatment with isotretinoin at low-dose (0.2–0.4 mg/kg/day), high-dose (0.5–1 mg/kg/day) and intermittent-dose (0.5–1 mg/kg/day only 1 week in 1 month) total testosterone levels significantly decreased in all groups. Total testosterone levels decreased from 2.55±2.81 to 1.96±1.98 (p<0.0001) in the whole group of patients [22]. Taking into account the effect of isotretinoin on testosterone blood levels, it can be assumed that, in addition to erectile dysfunction, other clinical manifestations of testosterone defiency may occur during treatment with isotretinoin, including gynaecomastia and decreased libido. The onset of gynaecomastia possibly related to treatment with isotretinoin, has been described in several case-reports [23-25]. Disproportionality in the databases of Lareb, WHO and EMA for these associations strengthens the proposed mechanism.

Table 4. Total reports of gynaecomastia and loss of libido / decreased libido associated with isotretinoin in the databases of Lareb [11], WHO [12] and EMA [13].

ADR	Number of reports	(Combined) ROR (95% CI)
gynaecomastia	Lareb: 6	8.6 (3.8 – 19.4)
	WHO: 102	1.8 (1.5 – 2.2)
	Eudravigilance: 30	1.5 (1.0 – 2.1)
loss of libido + libido decreased	Lareb: 3	2.9 (0.9 – 9.1)
	WHO: 77	1.3 (1.1 – 1.7)
	Eudravigilance: 42	1.8 (1.4 – 2.5)

Discussion and conclusion

Lareb received 7 reports of erectile dysfunction associated with the use of isotretinoin. Based on the information in the reports it can be assumed that erectile dysfunction happened repeatedly while using isotretinoin. Although two patients has been recovered after withdrawal (Case B and C), two other patients (Case F and G) has not been recovered 5 years and 2 months after the withdrawal of isotretinoin, respectively. These two cases do not support the supposed mechanism. The association

showed significant disproportionality in the databases of Lareb, EMA and WHO. The association has been described in literature and a plausible mechanism, decreased testosterone blood levels, can be assumed. In addition to erectile dysfunction, other clinical manifestations of testosterone deficiency like gynaecomastia and loss of libido has also been reported and described in literature. This strengthens the supposed mechanism. Our data suggests that treatment with isotretinoin can cause erectile dysfunction, possibly by causing testosterone deficiency. The association of erectile dysfunction with the use of isotretinoin is a new signal.

- Erectile dysfunction should be mentioned in the SmPC of isotretinoin.

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This signal has been raised on July 2015. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl