ENDOCRINE SIDE-EFFECTS OF ANTI-CANCER DRUGS

The impact of retinoids on the thyroid axis

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Abstract

Bexarotene (Targretin), approved since 1999 as a second-line treatment for late stage cutaneous T-cell lymphomas, has been shown to induce significant hypothyroidism through TSH suppression. This review revisits, through a case report, mechanisms by which retinoids repress the expression of *TSHB* gene as well as α *TSH* and *TRH* genes. It appears that retinoids suppress TSH independently from tri-iodothyronine. Bexarotene also differently affects the gene expression of deiodinases 1 and 2 as well as the peripheral clearance of thyroxine. These data might open new ways of research on the potential interaction between thyroid axis and endogenous retinoids.

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Introduction

In 2002, C Asteria published in the *European Journal of Endocrinology* a highlight paper entitled: 'Treatment with retinoid X receptor-selective ligand (bexarotene) may cause iatrogenic central hypothyroidism' which described a new mechanism of thyroid-stimulating hormone (TSH) suppression (1). More than 10 years later, taking advantage of the oncologists' and dermatologists' experience with bexarotene therapy and of the better understanding of the mechanisms of action of thyroid hormone and other nuclear receptor ligands, it is appropriate and timely to revisit the question.

Case report

Mycosis fungoides was diagnosed in a 67-year-old woman in September 2011. Since 2005, she had presented with prurigo and hypereosinophilia, initially treated with dermocorticoids and psoralen ultraviolet A (PUVA). In October 2011, she received methotrexate which had to be stopped because of clinical inefficiency and side effects. On November 7, 2011, bexarotene treatment was initiated. Initial daily dose of bexarotene was 300 mg and increased to 450 mg 1 month later. The patient complained of asthenia and of cold intolerance but her weight (52 kg; BMI: 21.6 kg/m²) did not

Invited Author's profile

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change. On January 9, 2012, at routine thyroid biological workup, serum free thyroxine (FT₄) was 3.5 pmol/l (normal range: 13.0–22.6), free tri-iodothyronine (FT₃) 1.6 pmol/l (normal range: 2.8–5.3) and TSH 0.86 mU/l (normal range: 0.29–3.80). Morning plasma cortisol and adrenocorticotropin were normal as well as the post-menopausal serum gonadotropin levels (luteinizing hormone, 10.1 UI/l (8.0–33.0); follicle-stimulating hormone, 37.9 UI/l (23.0–116); prolactin, 11.0 ng/ml (1.8–20.3); insulin-like growth factor 1, 120.2 µg/l (54.0–204.4); and growth hormone, 2.5 mU/l (<20)).

Before initiation of bexarotene treatment, thyroid tests were normal (TSH: 3.3 mU/l; FT₄: 13.0 pmol/l, FT₃: 3 pmol/l). Levothyroxine (L-T₄) was started at a daily dose of 50 µg and then progressively increased. On L-T₄, serum TSH remained undetectable throughout the bexarotene treatment period while FT₄ values remained infra-normal (7.0–11.0 pmol/l) until the L-T₄ dose was finally increased to 200 µg/day (4 µg/kg per day) with serum FT₄ reaching 16.7 pmol/l. Atorvastatin, 10 mg/day, had been prescribed along with bexarotene. However, because of disease progression, bexarotene was stopped in May 2013 and replaced by gemcitabine. L-T₄ was then withdrawn. Three weeks later, serum TSH was normal (3.08 mU/l) but FT₄ was low (9.4 pmol/l), FT₃ being high normal (5.0 pmol/l). Four months after the end of the bexarotene treatment TSH was normal at 2.4 mU/l; FT₄, 11.5 pmol/l (normal range: 9–19); and FT₃, 5.8 pmol/l (normal range: 2.6–5.8) (Fig. 1).

Background

Cutaneous T cell lymphoma

The gastrointestinal tract and the skin are the tissues more frequently affected with non-Hodgkin lymphoma. Cutaneous T-cell lymphomas represent ~80% of all primary cutaneous lymphomas. According to the WHO-EORTC classification, mycosis fungoides, an indolent proliferation of epidermotropic T cells, is the more frequent form (50%) of the disease while Sezary syndrome, the aggressive erythrodermic leukemic variant, is uncommon (2). Clinically, mycosis fungoides occurs mainly in adults, with a median age of 55–60 years at diagnosis and a male-to-female ratio of about 1.8. Mycosis fungoides is restricted to the skin, with slow progression over the years to infiltrated plaques, ulcerations, and cutaneous tumors. The TNM classification differentiates T1–3 (skin lesions: eczematous patches, localized or generalized plaques, cutaneous tumors), N1–3, and M0–1 stages (3).

Figure 1

Variation of thyroid parameters of the patient described in the case report, during time of treatment by bexarotene and levothyroxine (L-T₄) and 4 months after treatment withdrawal. Evolution of serum TSH (losange), FT₄ (triangle), and FT₃ (square) during and after bexarotene treatment at the dose of 300 mg/day first and 450 mg/day later. L-T₄ treatment was initiated at a dose of 50 µg/day 60 days after the beginning of bexarotene. The dose of L-T₄ was increased up to 200 µg/day (4 µg/kg per day). Notice that FT₄ decreased transiently after bexarotene and L-T₄ withdrawal despite the rise in TSH, only to normalize in response to the restoration of the pre-bexarotene TSH level 3 weeks after bexarotene had been withdrawn. Delayed normalization of FT₄ is likely related to the longlasting effect of bexarotene on the metabolic clearance of T₄. Normal values: TSH (0.29–3.80 mU/l), FT₃ (2.6–5.8 pmol/l), FT₄ (9–19 pmol/l).

Life expectancy is unaffected in T1–2 patients. The tumor–node–metastasis–blood-based staging criteria were revised in 2007 (4). The treatment algorithm of cutaneous T-cell lymphomas is based on the stage of the disease (4).

Retinoids

Retinoids, a group of structural and functional derivatives of vitamin A (retinol), are not only involved in vision as part of the rhodopsin molecule (the 11-*cis*-retinal) but also regulate complex gene networks involved in cell differentiation, proliferation, and apoptosis. Retinol is converted by alcohol dehydrogenase, then retinaldehyde dehydrogenase, to all-*trans*-retinoic acid, further isomerized to 13-*cis*-retinoic acid (isotretinoin) and 9-*cis*-retinoic acid in liver microsomes, depending on the levels of converting enzymes and cellular retinol-binding protein (5).

The biological activity of all-*trans*- and 9-*cis*-retinoic acid is mediated by two families of nuclear receptors that act as ligand-dependent transcriptional regulators: the retinoic acid receptors (RARA, -B, and - γ) and the retinoid X receptors (RXRA, -B, and - γ) which form either homodimers or heterodimers with numerous nuclear hormone receptors (vitamin D receptor, peroxisome proliferator-activated receptors (PPAR), the orphan liver X receptor (LXR), farnesoid X receptor, constitutive androstane receptor, and thyroid hormone receptor (TR) (6, 7). Although RARs bind, and are activated by, both 9-*cis*- and all-*trans*-retinoic acids, RXRs are exclusively activated by natural 9-*cis*-retinoic acid, unsaturated fatty acids such as docosahexaenoic, linoleic, linolenic, and arachadonic acid and other natural ligands or synthetic ligands called rexinoids (8). Recently, a number of synthetic rexinoids have been developed, among which LG100268 and LGD1069 (bexarotene) are highly RXR selective (9).

Bexarotene: actions and side effects

Bexarotene (Targretin) has been approved since 1999 by the US Food and Drug Administration as a second-line treatment for early- and late-stage refractory cutaneous T-cell lymphomas and the European Medicines Agency for the treatment of advanced stages (IIB–IVB) of the disease in Europe. It is the only rexinoid approved for clinical use. Bexarotene is prescribed orally. The starting dose is 150 mg/m² per day, to be adapted to clinical efficacy and tolerance. There is no evidence for any accumulation of the drug in the organism. It has a plasma peak 2 h after ingestion and a plasma half-life of 5–7 h (10, 11).

The mechanism of action of bexarotene on malignant T-cells is not completely understood, but the drug is thought to induce apoptosis through activation of the caspase-3 pathway and the poly(ADP-ribose) polymerase cleavage of (12) and/or inhibition of proliferation through the activation of the p53/73-dependent cell cycle pathway (13). The efficiency of bexarotene was also correlated with the inhibition of the mitogen-induced IL4 production by the peripheral blood cells (14). Bexarotene and other rexinoids are currently being studied as therapies for advanced lung, breast, and thyroid cancers (15) with, in the latter, restoration of RARB and RXR γ tissue expression and downregulation of NF- κ B target genes (16). Rexinoids have many other effects. Among these, they exert beneficial glucose-lowering and insulin-sensitizing effects as well as antiobesity actions in animal models of insulin-resistance and diabetes, and bexarotene improves cholesterol homeostasis and inhibits the development of

atherosclerosis in a mouse model of mixed dyslipidemia (17, 18). They also increase both hepatic liver oxidative metabolism through the increase in cytochrome P450, particularly the isoenzymes CYP4A, CYP2B1/2, and CYP3A levels, and the glucuronyltransferase activity (19). Finally, since bexarotene induces the transcription of apolipoprotein E and crosses the blood–brain barrier, it has been tested in a mouse model of Alzheimer's disease as a potential therapeutic agent to stimulate apolipoprotein E-induced clearance of β -amyloid with controversial conclusions (20).

The various side effects of bexarotene are listed Table 1. Some of them are nearly constant and appear to be dose dependent, likely related to the RXR agonist activity of the molecule. One of the initial phase II–III studies of the drug showed that 99% of the treated patients had experienced at least one significant adverse event (10). Central hypothyroidism (see the case report and below) and hypertriglyceridemia are the two expected side effects of bexarotene. Hypertriglyceridemia occurs with a median 5-week time interval after initiation of the treatment (21) in 82% of patients (10). It is severe (grade III and IV) in 11% of the patients, with pre-existing dyslipidemia being a risk factor (21). Hypertriglyceridemia (>8.5 mmol/l)-related pancreatitis is uncommon. Hypertriglyceridemia remains the more troublesome side effect despite combined lipid-lowering medications sometimes leading, in some patients, to bexarotene withdrawal. Triglyceride levels return to normal after treatment discontinuation. Elevated levels of LDL-cholesterol and low levels of HDL-cholesterol may also be observed in 30% of patients (10). Proper bexarotene treatment management and careful side-effects monitoring with routine laboratory tests minimize notably treatment drawbacks (22). As bexarotene is metabolized by cytochrome P450 3A4 (CYP3A4), interactions may occur with drug which affect CYP induction or activity (11). While the uncommon risk of hyperglycemia is unexplained, occurrence of severe hypoglycemia in insulin-treated patients is related to the bexarotene insulin sensitization effect (23). Table 1 lists the less common side effects of the drug.

Bexarotene and the thyroid axis

Background

It has been known for many years, in the context of vitamin A deficiency and/or supplementation trials, that vitamin A affects thyroid economy in several ways (24). Since 1995, a clearer picture has emerged, thanks to

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Table 1 Main bexarotene side effects. Table modified from (22).

Side effect	Prevalence (%)	Comments
Central hypothyroidism	29–100	Dose dependent, requires preventive levothyroxine substitution
Hypertriglyceridemia	82–100	Dose dependent, median interval from treatment initiation: 5 weeks, risk of acute pancreatitis (triglycerides > 8.5 mmol/l), requires preventive/curative lipid-lowering treatments
Increase in LDL-cholesterol	30	Usually easily manageable with lipid-lowering drugs
Decrease in HDL-cholesterol		
Liver toxicity, elevated liver enzymes	11–20	Dose dependent, bexarotene discontinuation if elevation of transaminases greater than fivefold
Drug interactions with inhibitors or activators of the cytochrome P450 enzymes and GT	–	Dependent on drugs combination
Headache, asthenia	16–20	–
Skin eruption, pruritus, mild phototoxicity	8–13	At treatment initiation
Leucopenia (neutropenia)	6–11	Late occurrence, especially in combination with chemotherapy
Uncommon	< 5	Bexarotene enhances insulin action
GI symptoms		
Hypoglycemia in insulin-treated patients		
Hyperglycemia		
Teratogenicity	–	Bexarotene contraindicated in women of childbearing age without contraception

studies of the effects of available natural or synthetic vitamin A derivatives, including retinoids, with narrow target specificity allowing for more specific action analysis. In 1978, Morley *et al.* (25) observed that vitamin A-deficient rats had significantly higher serum T_4 and T_3 levels than controls and that their pituitary TSH content was also increased suggesting a pattern of central hyperthyroidism. Breen *et al.* (26) observed that vitamin A deficiency led, in normal but not in hypothyroid rats, to a twofold increase in pituitary TSH β mRNA levels which returned to normal 18 h after treatment with retinoic acid. Interestingly, there was no synergistic effect of the co-administration of retinoic acid and T_3 on the TSH β mRNA decrease in vitamin A-deficient animals (26). In 1997, Coia *et al.* (27) found that rats, either euthyroid or hypothyroid, treated with retinoic acid, showed a decrease in spontaneous basal TSH levels and TSH responses to TRH. In a quite different setting, data with similar meaning were recently reported in mildly iodine-deficient children in whom vitamin A (retinyl palmitate) supplementation decreased excess TSH stimulation thereby reducing the risk of goiter (28).

Bexarotene and the inhibition of TSH secretion

The occurrence of symptomatic central hypothyroidism in a patient with cutaneous T-cell lymphoma treated with

bexarotene led Sherman *et al.* (29) to study the thyroid function of 27 patients with the same disease participating in the open-label study of high-dose (> 300 mg/m² per day) oral bexarotene. Severe central hypothyroidism occurred in 70% of these patients. Symptoms were usually poor (fatigability, cold intolerance, impaired cognition, constipation). Mean serum TSH declined from 2.2 to 0.05 mU/l, and mean FT₄ from 12.9 to 5.8 pmol/l during bexarotene treatment. Correlation between nadir-to-baseline TSH ratio and the dose of bexarotene suggested a dose–effect relationship. After bexarotene discontinuation, among the 10/11 patients with normal thyroid function before bexarotene treatment, serum TSH concentrations returned to normal in nine as early as 8 days (29). In 1999, Dabon-Almirante *et al.* (30) reported on a woman with advanced cervical cancer treated with 9-*cis*-retinoic acid in whom TSH was suppressed and normalized spontaneously after drug withdrawal. Subsequently, Golden *et al.* (31) carried out a randomized, double-blind, crossover trial in six normal subjects who received a single dose of bexarotene, 400 mg/m² of body surface area, or placebo. Serum TSH level had decreased as early as 12 h after drug administration, the nadir being reached at 24 h (0.32 ± 0.02 vs 1.48 ± 0.19 mU/l), and remained lower than in controls at 48 h (0.47 ± 0.06 vs 1.80 ± 0.2 mU/l). FT₄ and FT₃ indexes remained lower than in controls for 48 h. Serum prolactin and cortisol were not affected, as well as

fasting and post-prandial blood glucose, triglyceride, insulin and free fatty acid levels (31), in accordance with our case report. To our knowledge, bexarotene does not affect the levels of the other pituitary hormones. Indeed, UK consensus statement on safe clinical prescription of bexarotene does not recommend exhaustive pituitary testing (11).

Bexarotene and the peripheral metabolism of thyroid hormones

Effects on thyroid hormone biodisponibility have also been suggested to explain the relative hypothyroidism observed in patients treated with bexarotene. Smit *et al.* studied ten athyreotic thyroid cancer patients with iodine uptake-negative pulmonary metastases who were on a 6-week redifferentiation treatment protocol with 300 mg/day bexarotene. During the bexarotene treatment protocol, the dose of L-T₄ treatment was unchanged. Bexarotene and L-T₄ were taken 12 h apart to prevent absorption interference. A marked decrease in serum total T₄ (56% of baseline value) without alteration in serum TBG, as well as in serum FT₄ (47%), total T₃ (69%), and rT₃ (51%), was observed in all patients, suggesting a bexarotene-induced increase in thyroid hormone metabolism. Serum TSH remained unchanged despite the decrease in thyroid hormone serum concentrations. The parallel decrease in T₄, T₃, and rT₃ together with the modest increase in T₃:rT₃ ratio suggested to the authors that bexarotene did not significantly affect the three deiodinase activities (D1, D2, and D3). In contrast, serum T₄ sulfate decreased to 70% of basal value while the T₄ sulfate:FT₄ ratio increased, which suggests an induction effect of bexarotene on the T₄ sulfation and, possibly, glucuronidation pathways (32). These data are in line with the known activation by rexinoids of the liver metabolic oxidative enzymes as well as glucuronidation resulting in an increase of thyroid hormone metabolic clearance. However, at variance with these observations, rexinoid-induced modifications in deiodinase levels have indeed been reported in cell and animal models. In mice treated for 3 days with LG268, liver D1 mRNA and activity were found to be increased (5). In the pituitary, D2 mRNA was decreased but D2 activity remained unchanged. Interpretation of the pituitary data has to combine the direct negative effect of LG268 on the expression of the D2 gene and the indirect post-translational positive one on the D2 protein activity, the intracellular degradation of which is slowed by the T₄ decrease resulting from the LG268 suppression of TSH. In the brain, D2 mRNA was

unchanged while D2 activity was increased, likely also as a consequence of the T₄ lower levels. Rexinoid suppression of the pituitary D2 gene expression, confirmed on the thyrotrope-derived pituitary cell line TAT1, appears tissue specific because it is not observed in the brain. In addition, rexinoid effect on D2 gene expression is RXR-selective as it is not observed with a selective RAR agonist or in mice with invalidated RXR γ (5).

As a whole, bexarotene-induced increase in peripheral clearance of thyroid hormone contributes to the drug-induced hypothyroidism. It also could explain the requirement for L-T₄ doses higher in the treatment of bexarotene-induced hypothyroidism than hypothyroidism related to other causes. Figure 2 depicts the various levels of action of bexarotene on the thyroid economy.

Molecular aspects of the bexarotene-induced central hypothyroidism

RXR γ is the isoform implicated in bexarotene-induced central hypothyroidism ► 13-*cis*-retinoic acid, isotretinoid, a RAR agonist, has no effect on serum TSH levels, which confirms that the effects of retinoids on TSH are not mediated through RAR (33). In contrast, 9-*cis*-retinoic acid could suppress serum TSH in human (30). Expression of the three RXR isoforms is unevenly distributed among tissues. While RXRA and RXRB are expressed ubiquitously including in the anterior pituitary, RXR γ expression is strongly restricted to skeletal muscle, heart, brain, thyroid, and pituitary (34, 35), the RXR γ 1 isoform being specifically expressed in the pituitary gland, especially in the thyrotrope cells, in mouse as well as man (36, 37, 38). Mice with inactivation of the *Rxr γ* gene disclose elevated levels of T₄ and TSH and are relatively resistant to exogenous T₃, a phenotype consistent with thyroid hormone resistance, suggesting the specific involvement of the RXR γ isoform in the regulation of pituitary TSH production (39). However, *Tshb* mRNA suppression by rexinoids in this model of mice lacking *Rxr γ* is not an all-or-none phenomenon. RXR is required at low dose of rexinoids, but other receptor isotypes can mediate the suppressive effect at high doses (5). On the same line of evidence, a selective RXR antagonist, LG101208, *in vitro* induces a 71–81%, at 24 and 48 h, increase in *Tshb* mRNA levels in TAT1 mouse thyrotrope cells, as well as an increase (53–47%) in the common glycoprotein α -subunit and D2 mRNA levels (40). In mice treated with LG101208, serum total T₄ levels and T₄:TSH ratio were significantly higher, serum TSH levels being slightly, but not significantly, higher than in control mice, a pattern compatible with a new thyroid

Figure 2

Central and peripheral thyroid effects of the RXR-selective bexarotene. Thyroid hormone exerts its actions through nuclear TR which behave as ligand-inducible transcription factors. TR acts through binding to DNA on specific sequence, the TRE. T_3 negatively controls at transcriptional level the production of hypothalamic TRH and pituitary TSH. TR binds to corresponding nTRE as a monomer. Bexarotene, the RXR-selective ligand, induces central hypothyroidism by repressing *TSH β* subunit expression through a specific binding site, RXRE, distinct from the nTRE. For target genes regulated positively by T_3 , TR usually binds to positive TRE as heterodimer with RXR. TR/RXR heterodimers are considered as non-permissive, i.e. dimer activation cannot be obtained through the sole binding of a RXR agonist to the heterodimer. By contrast, permissive dimers, such as PPAR/RXR and LXR/RXR, are activated by a RXR agonist as bexarotene. This mechanism may explain the hyperglycemia associated with bexarotene. Additionally, bexarotene is thought to interfere with thyroid hormone biodisponibility through liver oxidative enzyme activation and alteration in the expression and activity of the D1 and D2 deiodinases. TR, RXR, PPAR, and LXR ligand symbols: T_3 (circle); bexarotene (losange); square and triangle: others.

‘set point’ configuration. Pituitary *Tshb* and A-subunit mRNA levels were higher, but pituitary D2 levels were not different between treated and untreated animals (40). Altogether, these results highlight the potential role of RXR γ in the control of pituitary TSH production.

Bexarotene and the suppression of the *TSH β* gene promoter activity ► Several studies, both *in vivo* and *in vitro*, have demonstrated the suppressive effect of both all-*trans*- and 9-*cis*-retinoic acid on the specific *TSH β* gene promoter (5, 9, 26, 37). Since the transactivation mediated by the binding of T_3 to TR is facilitated by the formation of TR/RXR heterodimers, the first question arising had been whether bexarotene suppresses *TSHB* expression through binding to TR/RXR heterodimers (Fig. 2). The question is all the more appropriate as the mechanisms of the negative gene regulation by T_3 are less well understood than those involved in positive regulation. At least three different models for the negative regulation by T_3 have been proposed (41). For the regulation of *TSHB* expression, it is proposed that the unliganded TR bound minimally to the DNA of the *TSHB* negative thyroid hormone response element (nTRE) shifts to a strong binding in the presence of T_3 , with the recruitment of coregulators, possibly under TR conformation allosteric changes induced by the nTRE upon TR- T_3 binding (42, 43, 44, 45).

Two lines of experimental data strongly suggest that bexarotene and similar rexinoids induce central hypothyroidism by direct binding of liganded RXR to specific response elements independently from any interaction with TRE:

- retinoids suppress *TSHB* promoter activity through the -200 to -149 bp region of the mouse and rat promoter (37, 46), which is in sharp contrast to the location close to the transcription start sites of the TREs which mediate the negative effects of T_3 (37, 46, 47) and
- in mice deficient in the TRB isoform (TRB $^{-/-}$) of the TR, treatment with a RXR agonist induced a potent and rapid suppression of serum TSH and T_4 (48).

It should be reminded, however, that the molecular mechanisms involved in both the TR and RXR-negative regulations of the *TSHB* gene are still unclear, notably in what concerns their mutual interactions and the implication of the various endogenous coregulators within thyrotrope cells (49, 50). Similarly, it is still not clear whether the regulation of the *TSHB* promoter activity by rexinoids and T_3 is additive or synergistic.

In addition to the above-described effect, a likely non-genomic rexinoid action on TSH secretion has been described by Liu *et al.* (9). In rats, a fall in serum TSH was apparent as early as 30 min after LG268 administration, with the nadir at 4–8 h, contrasting with the absence of reduction in pituitary *TSHB* mRNA and TSH protein at 2 h after LG268 administration. In the same experiment, TRH-stimulated TSH secretion was blunted which, together with the decrease in serum TSH, would suggest a rexinoid-induced alteration in the secretion/release process of the hormone, the mechanism of which is unknown. It is suggested that the time interval between rexinoid administration and pituitary *TSHB* mRNA and TSH content determination was too short for a change to be observed (9).

Does bexarotene influence the glycoprotein α -subunit and TRH gene expressions?

In TAT1 cell line, the rexinoid LG268 decreased mRNA levels of the glycoprotein α -subunit along with those of *TSHB* and D2 as mentioned earlier. Accordingly, pituitary α subunit mRNA levels, as those of *TSHB*, were higher in mice treated with the RXR antagonist (40), indicating that the α subunit and *TSHB* promoters share, at least partially, the same regulation.

Thyroid hormone control is also exerted on hypothalamic TRH production. nTREs have been identified in the human *TRH* gene promoter as three separate half-sites which act in combination for full promoter repression (51). Although two of these binding sites only bind TR monomers, the third one is able to bind TR monomers and homodimers or TR/RXR heterodimers (51). RXRs' influence on T_3 -mediated repression of *TRH* gene has been suggested by *in vitro* studies (51, 52, 53). *In vivo* administration of LG268 did not change the hypothalamus levels of *TRH* mRNA despite the concomitant decrease in serum TSH and T_4 which, nevertheless, suggests some degree of suppression (5). Accordingly, in animals treated with the RXR antagonist, the levels of hypothalamic pre-proTRH mRNA levels were not different from controls despite increased T_4 levels also indicating that the upregulation of the *TRH* gene expression by rexinoids cannot be excluded (40).

Altogether, it has been demonstrated that bexarotene is responsible for central hypothyroidism essentially through direct binding on specific regulatory regions of the *TSHB* gene, with coordinated effects on the α subunit and TRH production. It is unlikely that other bexarotene side effects, such as dyslipidemia, would result from direct

alteration of the thyroid economy in the periphery. Rather, bexarotene-induced dyslipidemia is related to the permissive effect of RXR–LXR (18) and PPAR α /RXR heterodimers (54, 55). Indeed, bexarotene has been shown to activate hepatic lipogenic genes such as *SREBP1c*, *FAS*, *FAE*, and *SCD1*, leading to increased triglycerides production via the RXR–LXR heterodimer in a dose-dependent manner (18). Recently, polymorphisms associated with bexarotene-induced high-grade hypertriglyceridemia were identified with potential in predicting bexarotene-improved survival response (56).

Recommendations for bexarotene treatment management

Before initiating bexarotene therapy, patients with a past history of hyperlipidaemia, diabetes or cardiovascular disease, and abnormal thyroid function should be identified. Concomitant medications affecting liver oxidative enzymes should be monitored appropriately. Full blood count, urea and electrolytes, liver and thyroid function tests, serum lipids, glucose, and creatinine kinase should be assessed (57). According to the recent UK recommendations, occurrence or worsening of hypertriglyceridemia should be prevented with fenofibrate or, if contraindicated, a statin treatment initiated 1 week before bexarotene treatment. Blood lipids should be tested on a weekly basis until control is obtained (11).

$L-T_4$ may be started at the initiation of bexarotene (25–50 μ g/day, with caution in patients with cardiovascular disease) or as soon as hypothyroidism is detected (50–100 μ g/day). Serum FT_4 (and T_3), not TSH, should be measured monthly until doses of bexarotene and $L-T_4$ have been stabilized. $L-T_4$ treatment should be adapted in order to maintain FT_4 level at the pre-bexarotene value. As it is obvious in the case report, the dose of $L-T_4$ can be as high as 200–250 μ g/day (58). Because of the usual prolonged effect of the induction of liver oxidative enzymes, discontinuation of the $L-T_4$ treatment should be progressive after bexarotene discontinuation, guided on serum FT_4 controls, as illustrated in the case report.

Conclusion

Bexarotene, through its nuclear receptor RXR, is able to regulate negatively the expression of the *TSH β* gene and, at a lesser degree, of α *TSH* and *TRH* genes leading to central hypothyroidism, an effect observed in nearly 100% of the patients treated with 150 mg/m² per day, warranting routine concomitant $L-T_4$ treatment. Bexarotene also

affects the expression of deiodinase *D1* and *D2* genes positively or negatively in the liver and pituitary respectively. In addition, bexarotene increases the metabolic clearance of T_4 . The central suppression of TSH appears independent from that of T_3 thus providing a still theoretical way to directly interfere with the secretion of TSH in specific situations of resistance to thyroid hormones or thyroid cancer. The pharmacological rexinoid-mediated TSH alteration could also suggest a physiological role of endogenous RXR ligands, such as the polyunsaturated fatty acids, in the modulation of the thyroid axis set-point, well in line with current studies on the metabolism–thyroid axis interactions.

Declaration of interest

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