Retinoids in Clinical Use

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Abstract: Retinoids have been investigated for their therapeutic potential for the past 3 decades. They have a reputation for being both beneficial in the treatment of several diseases and detrimental due to toxic and/or teratogenic side effects. The purpose of this review is to highlight retinoids that are currently used in the clinic. We also discuss their mechanisms of action and research strategies to develop new and safer retinoid-based therapies.

Key Words: Retinoids, rexinoids, retinoic acid metabolism blocking agents (RAMBAs), RAR/RXR, clinical utility.

INTRODUCTION

Retinoids are a class of polyisoprenoids that are derived by oxidative cleavage of β-carotenes of plant origin to yield vitamin A (retinol). Dietary sources of vitamin A include eggs, milk, butter and fish-liver oils [1,2]. Retinoids are essential for embryonic development and play important physiological functions, particularly in the brain and reproductive system, by regulating organogenesis, organ homeostasis, and cell growth, differentiation and apoptosis [1,2]. The naturally occurring and synthetic retinoids are currently the subject of intense biological interest stimulated by the discovery of retinoid nuclear receptors and the realization of these compounds as non-steroidal small-molecule hormones [3]. However, it should be stated that before the discovery of the nuclear retinoid receptors, a number of therapeutically useful retinoids were identified [4,5]. Indeed, most retinoids that are currently used in dermatology and in oncology, such as all-trans-retinoic acid (ATRA, tretinoin), 13-cis retinoic acid (13-CRA, isotretinoin), etretinate and acitretin, were discovered by chemical modifications on the basis of vitamin A structure and by biological evaluations in suitable pharmacological models. This review pre-supposes familiarity with the retinoid field in general. For those seeking more background information, many recent and comprehensive reviews are available [2, 6-8]. Our purpose here is to provide the reader with an astute review of retinoids that are in clinical use and also those retinoids that are currently in clinical trials. This review mainly is based on perspectives, reviews and abstracts published in the last 12 years up to December 2005. Most of the original articles cited were also consulted.

MECHANISM OF ACTION OF RETINOIDS AND RETINOIC ACIDS

With current knowledge, the pleiotropic action of retinoic acids (RAs) and retinoids might be explained mechanistically by the actions of the six known nuclear receptors, the retinoic acid receptors (RARα, β, γ) and the retinoid X receptor (also called rexinoids, (RXRα, β, γ).[2,3,9,10] Each of these receptors are encoded by distinct genes and are members of the steroid/thyroid hormone receptor superfamily. It is also thought that each receptor mediates a set of unique biological functions in certain cell or tissue types. ATRA (Fig. **1**) is the natural ligand of the RARs, while 9-CRA is the ligand for the RXRs and it also has a high affinity for the RARs. The binding of the other ATRA stereoisomers, 11-cis-retinoc acid (11-CRA) and 13-CRA to these receptors is still unclear. However, because of the reported antitumor efficacy of 13-CRA [11-15], it is plausible that 13-CRA is isomerized intracellularly to ATRA, or it may act without obvious interaction with the known retinoid receptors. Clearly, more research is needed in this area.

Most of the pleiotropc activities of the RAs and other retinoids are elicited by the binding of these agents to the RAR site of RAR-RXR heterodimers. RXRs are the silent partners of the RARs, as the RXR ligands alone are unable to activate the RAR-RXR heterodimers. However, recent studies using RAR- and RXR-selective ligands have revealed that the RXR ligands allosterically increase the potencies of the RAR ligands [16-18]. Furthermore, RXRs form heterodimers with various nuclear receptors, such as estrogen receptors (ERs), vitamin D_3 receptors (VDRs), thyroid hormone receptors (TRs), peroxisome proliferators-activated receptors (PPARs), liver X receptors (LXRs), and farnesoid X receptors (FXRs). Because of these unique properties of the RXRs, the RXR ligands are able to modulate the activities of other hormone receptors, in addition to their retinoidal activities [19].

These receptors, as heterodimers (RAR/RXR) or homodimers (RXR-RXR), function as RA-inducible transcriptional regulatory proteins by binding to DNA regions called retinoic acid response elements (RAREs) or retinoid X response elements (RXREs) located within the promoter of target genes. RAREs consist of direct repeats of the consensus half-site sequence AGGTCA separated most commonly by five nucleotides (DR-5), whereas RXREs are typically direct repeats of AGGTCA with one nucleotide spacing (DR-1). In

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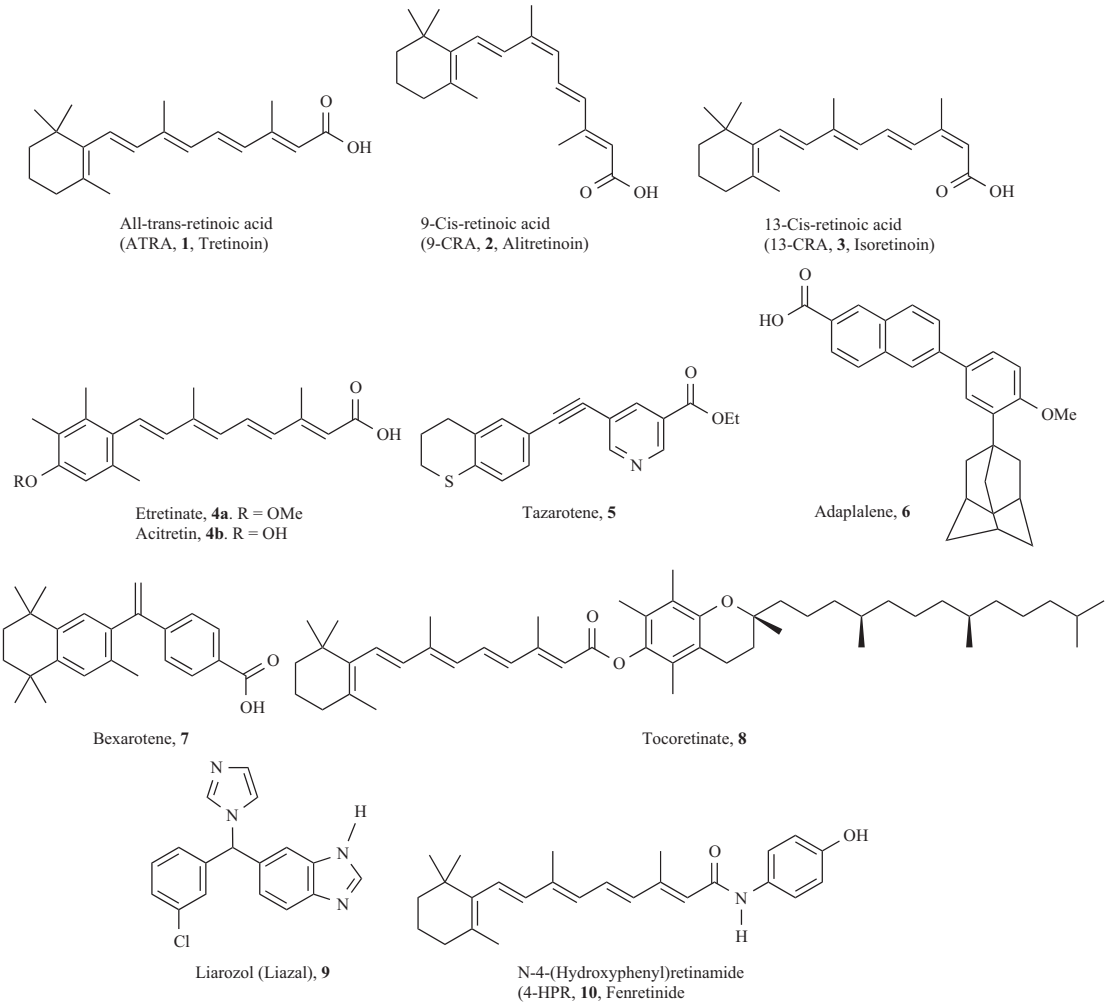

Fig. (1). Chemical structures of retinoids and related compounds.

the absence of ligand (ATRA or 9-CRA) the apo-heterodimer (RAR-RXR) binds to the RARE in the promoter of the target genes and RAR recruits co-repressors (CoRs) such as nuclear receptor co-repressors (NCoR) or and silencing mediator for retinoid and thyroid receptors (SMRT). These co-repressors function by recruiting histone deacetylase complexes (HDACs), causing target gene repression due to compaction of chromatin, making DNA inaccessible to the transcriptional machinery. However, in the presence of ATRA or an agonist, there is a confor-mational change in the structure of the ligand binding domain that results in destabilization of the CoR-binding with concomitant recruitment and interaction with co-activators (CoAs). Some co-activators interact directly with the basal transcriptional machinery to enhance trancscrip-tional activation, while others encode histone acetyl transferase (HAT) activity. HAT acetylates histone proteins, causing the opening of the chromatin and activation of transcription of the associated gene. Other complexes, such as the thyroid receptor associated protein are also involved in this process. It should be stated that, whereas the RARα is involved in myeloid leukemias, a growing body of evidence indicates that RARβ is involved in a diverse range of solid tumors [2]. For more details on the mechanism of action of ATRA, reviews by Chambon [9] and Altucci and Gronemeyer [2] should be consulted.

RETINOIDS IN THE CLINIC AND IN CLINICAL INVESTIGATIONS

Although retinoids have shown immense translational potential because of their activities *in vitro* and *in vivo*, their use in the clinic has resulted in limited responses. Part of the problem is that most of the retinoids studied in the clinic (Table **1**) were stand-alone therapies and not geared towards an optimal therapeutic regimen where they are used in combination with other therapeutic or disease-modifying agents. In addition, most of the promising newer generation of receptor and/or function selective retinoids has not yet been investigated in the clinic [7,8].

Table 1. Retinoids in the Clinic or in Clinical Trials

Compound (Drug Name)	Indication	Pharmacology	Clinical Status	Company Name
All-trans-retinoic acid (1) (Tretinoin)	Acne, Photodamage, Acute promyelocytic Leukemia (AML)	RAR agonist, Protein synthesis antagonist, microbial collagenase inhibitor	Launched	AP Pharma, Johnson & Johnson, Hoffmann-La Roche, Myland Labs.
9-cis-retinoic acid (2) (Alitretinoin)	Psoriasis, Kaposi's sarcoma, AML	RAR and RXR agonist, apoptosis agonist	Lunched	Ligand
13-cis-retinoic acid (3) (Isotretinoin)	Acne	RAR agonist, Protein synthesis antagonist, microbial	Lunched	Hoffmann-La Roche
Etretinate (4a) Acitretin (4b)	Breast cancer, non-small cell lung cancer, Kaposi's sarcoma, T-cell lymphoma	RXR agonist	Lunched	Hoffmann-La Roche
Tazarotene (5)	Acne, psoriasis, cancer	RAR_ agonist	Lunched	Allergan
Adapalene (6)	Acne, psoriasis	RAR agonist, Protein synthesis antagonist, microbial collagenase inhibitor	Lunched	Galderma
Bexarotene (7)	Psoriasis, keratosis, eczema, head & neck, renal, prostate, ovarian and colorectal cancers	RXR agonist	Lunched	Ligand
Tocoretinate (8)	Ulcer	RAR antagonist, Protein synthesis antagonist, microbial collagenase inhibitor	Lunched	Nisshin Pharma
Liarozol (9), (Liazal)	Laminar ithciosis	Inhibitor of ATRA catabolism	Lunched	Johnson & Johnson
Fenretinide (10)	Prostate & CNS cancer, breast cancer chemoprevention	RAR agonist, Apoptosis agonist	Phase III	Johnson & Johnson

It is now generally believed that retinoids have promising potential for a number of indications, including various dermatological diseases, cancers, ulcer, type II diabetes and HIV infection. However, the reality is that these agents are only currently effective in man for the treatment of various dermatological diseases such as acne, psoriasis and other keratinizing dermatoses and also in the treatment of a few types of cancers. We will focus our attention on retinoic acids and derivative(s), synthetic RAR agonist and antagonist and then those molecules able to increase the endogenous retinoic acid by inhibiting the cytochrome P450-mediated catabolism of retinoic acid, also known as the retinoic acid metabolism blocking agents (RAMBAs). Specifically, we will discuss the clinical agents (see Fig. **1**), including all-*trans* retinoic acid (ATRA, **1**), 9-*cis*-retinoic acid (9-CRA, **2**), 13-*cis*-retinoic acid (13-CRA, **3**), etretinate/ acitrtine (**4a/4b**), tazarotene (**5**), adapelene (**6**), bexarotene (**7**), tocoretinate (**8**), liarozole (**9**) and those in clinical trials, including N-4-(hydroxyphenyl)retinamide (4-HPR, fenretinide, **10**). The recent review by Berrie and Goldhill [3] provides a comprehensive list of retinoids and related compounds in the clinic and in clinical trials.

All-*trans*-retinoic Acid (ATRA, Tretinoin, 1)

Tretinoin (**1**) is an RARα,β,γ agonist and was the first retinoid approved for the treatment of acne and has been in clinical use for almost 3 decades. It is used as a monotherapy in patients with non-inflammatory comedones, and in combination with other topical or systemic drugs in mild, moderate and severe inflammatory acne [21,21]. Tretinoin acts by increasing the turnover of follicular epithelial cells and by accelerating the shedding of corneocytes. These processes help normalize keratinization, which leads to drainage of comedones and inhibition of new comedone formation. A major concern with the use of early formu-lations of tretinoin was excessive skin irritation associated with its hydro-alcoholic vehicle and the high concentration of the drug. This side-effect has now been corrected by use of various creams/gels vehicles, and with low drug concentrations (e.g., 0.0025, 0.05 and 0.01%) [22,23]. Topical formulations of ATRA are currently used for treatment of acne, psoriasis and ichthyosis [24].

Best defined among the clinical oncological application of retinoids is the use of ATRA for treatment of acute promyelocytic leukemia (APL). Oral administration (45 mg/m^2/day p.o.) of this drug to APL patients is currently approved in several countries worldwide. More than 90% of APL patients achieve complete remission with ATRA therapy [25,26]. The basis for the dramatic efficacy of ATRA against APL is the ability of pharmacological doses of ATRA to overcome the repression of signaling caused by the PML-RARα fusion protein at physiological ATRA concentrations. Restoration of signaling leads to differentiation of APL cells and then to postmaturation apoptosis [17]. Several randomized clinical trials have now defined the utility of ATRA as maintenance therapy [28,29] and also the benefits

of combining ATRA with chemotherapy [30]. The National Cancer Institute (USA) is currently evaluating ATRA as an anticancer agent in phase II trials for brain, head and neck, and prostate caners [6].

9-*Cis*-retinoic Acid (9-CRA, Alitretinoin, 2)

9-Cis-retinoic acid has been detected in humans [31] and was the first RAR/RXR pan-agonist discovered [32-34]. It is the only retinoic acid isomer not approved for the common dermatological diseases. However, it has recently been launched in the USA as adjuvant topical treatment of AIDS-associated Kaposi's sarcoma [35-39]. This agent is the first RXR ligand to be approved for the treatment of a dermatological disease. In a randomized study with 268 AIDS-associated Kaposi's sarcoma patients, 35% treated with alitretinoin (0.1% gel) had a positive response, compared with 18% treated with vehicle gel irrespective of the number of concurrent anti-retroviral therapies [35]. 9-CRA is in clinical trials for the treatment of various cancers, including breast cancer [40], renal-cell carcinoma [41,42] and squamous-cell carcinoma [43-45].

13-*Cis*-retinoic Acid (Isotretinoin, 13-CRA, 3)

13-CRA is a metabolite of ATRA [46] that binds poorly to the RARs. Recent studies suggest that 13-CRA is a prodrug, activated in human sebocytes *via* a selective intracellular isomerization to high levels of ATRA and subsequent binding to RARs [47]. This agent has been available in topical formulations in Europe since the early 1970s for the treatment of acne. In the USA, oral isotretinoin greatly advanced the treatment of severe acne after an important discovery by Peck and Yoder [48]. Isotretinoin gained approval from the US Food and Drug Administration (FDA) for the treatment of resistant nodular acne in 1982 [49]. Numerous clinical studies do not show a fundamental difference between 13-CRA and ATRA [50-52], although the former is apparently better tolerated and it is the only retinoic acid isomer used in systemic form [53]. On the basis of several clinical trials (reviewed in reference [54]), systemic isotretinoin may be considered as an alternative drug in some dermatological diseases unresponsive to conventional therapy. Nevertheless, more randomized clinical trails to determine the role of systemic isotretinoin therapy in dermatological diseases, including skin cancers other than acne are required. Isotretinoin also represents a potentially useful drug in many dermatological diseases other than acne and also skin cancers, due to its immunomodulatory, anti-inflammatory and anti-tumor activities [54].

Etretinate (4a, Ethyl all-*trans*-3,7-dimethyl-9-(4-methoxy-2,3,6-trimethylphenyl)nona-2,4,6,8-tetraenoate) and Acitretin (4b, all-*trans*-3,7-dimethyl-9-(4-methoxy-2,3,6-trimethylphenyl)nona-2,4,6,8-tetraenoate)

Etretinate (**4a**) is considered as a second-generation retinoid with a characteristic substituted aromatic ring in place of the substituted cyclohexenyl ring in retinoic acids. It was first lunched by Hoffmann-La Roche in the USA in 1982 as the first systemic retinoid for psoriasis. Etretinate was replaced by its hydrolyzed metabolite free acid–acitretin (**4b**) in 1997. Acitretin was found to be clinically as effective as etretinate, but with a much shorter elimination half-life, advantageous for clinical use. Acitretin does not bind to, but activates, the RARs [55], and it has a high affinity for both cellular retinoic acid binding proteins I and II (CRABP I and II) [56]. Systemic treatment with acitretin is effective in several disorders of keratinization, due to its action in promoting keratinocytes differentiation in several skin disorders [57]. A review of acitretin as a systemic retinoid for the treatment of psoriasis has recently appeared [58]. Oral acitretin is currently being investigated in several clinical trials for the prevention of skin cancers in solid organ transplant patients [59-61]. Paradoxically, in spite of the similar therapeutic efficacies of acitretin and etretinate, the latter has been reported to succeed in cases where acitretin has failed [62]. In addition, a recent study reported the successful use of etretinate for long-term management of a patient with cutaneous-type adult T-cell leukaemia/lymphoma [63]. Reports of this nature may warrant the resurgence of etretinate.

Tazarotene (Ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)-ethynyl] Nicotinate, 5, Tazarac®, Allergan, Inc.)

Tazarotene (**5**) was first approved in 1997 by the FDA for the treatment of acne [64], but it is also currently used for the treatment of plaque psoriasis [65] and photodamage [66]. It is a synthetic acetylinic retionoid that is readily hydrolyzed to its active form, tazarotenic acid in keratinocytes. Unlike its parent compound, tazarotenic acid has the ability to bind and activate RARβ and RARγ (RARβ> RARγ) with less effect on RARβ and, no effect on the RXRs [67]. However, because RARβ is not expressed in human keratinocytes, the effect of this drug on the major cell type of the epidermis is clearly attributed to its interaction with RARγ. Through regulation of gene expression in a specific manner, tazarotenic acid modulates abnormal differentiation of keratinocytes, increased keratinocyte proliferation and inflammation [64]. Clinical responses are seen after 2 weeks, with significant clearing after 6-12 weeks of treatment with topical gel or cream formulations of tazarotene [68]. Combination of tazarotene with topical corticosteroids of low potency appears to increase overall therapeutic potential with reduced side effects, such as local skin irritation, erythema, and burning sensation [69]. A review of the use of topical tazarotene in the treatment of plaque psoriasis has recently been published [70].

Following a clinical study which suggested that tazarotene may be effective treatment of cutaneous basal cell carcinoma (BCC) [71], a recent study of 30 patients with small superficial and nodular BCC was conducted to assess the efficacy and mechanism of action of tazarotene (0.1% gel). Overall, 76.7% of treated tumors showed > 50% regression, while complete healing was observed in 46.7% of all treated BCC. Induction of tazarotene-induced BCC regression was attributed to synergistic RARβ-dependent anti-proliferative and pro-apoptotic activities [72].

Adapelene (6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid, 6, Differin®, Galderma Labratories)

Adapelene (**6**) is a naphthoic acid derivative with a methoxyphenyl adamant side chain and is a commonly used

anti-acne drug [73]. Similar to the action of tazarotene in its hydrolyzed form - tazarotenic acid, adapelene interacts selectively with RARβ and RARγ, and its activity on proliferation and differentiation can be blocked by a RARγ antagonist [74]. In addition, adapelene has anti-inflammatory potential due to its anti-AP1 activity [74]. Although its efficacy is similar to that of other retinoids, it has an improved therapeutic ratio due to its better tolerance [reviewed in ref 75].

Bexarotene (7, 4-[1-(5,6,7,8-tetrahydro-3,5,58,8-pentamethyl-2-naphthalenyl)ethenyl]benzoic Acid)

Bexarotene (**7**) is a selective RXR agonist (classified as a rexinoid) whose exact mechanism of action in cancer therapy and chemoprevention is poorly understood [8]. In a multinational phase II-III clinical trials, oral bexarotene (300 mg/m2/day) showed 55% response rate in patient with refractor advanced stage cutaneous T-cell lymphoma (CTCL) [76]. Bexarotene (1% Targretin gel) is approved for the topical treatment of cutaneous lesions in patients with state 1A and 1B CTCL who have not tolerated other therapies or who have refractory or persistent disease [77,78]. The ability of bexarotene to activate RXRs and their heterodimer partners results in modulation of gene-expression pathways, which ultimately modulate converging signaling pathways responsible for cell differentiation and apoptosis [79]. This multi-targeted approach of mediating cell differentiation, apoptosis, and proliferation suggest that bexarotene may be particularly active in the treatment of malignancies, especially in combination with chemothera-peutic agents. Thus, following acceptable phase II response rates (25%) in combination with cisplatin and vinorelbine in non-small-cell lung cancer (NSCLC) [80,81], oral bexa-rotene in combination with paclitaxel and carboplatin or vinorelbine is currently being evaluated in multi-center phase III studies in previously untreated patients with NSCLC patients [82]. A recent preclinical study by Yen and Lamph suggests a role of bexarotene in combination with paclitaxel in prevention and overcoming acquired drug resistance in advanced prostate cancer [83].

Tocoretinate (Tretinoin tocoferil, (±)-3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyl-tridecyl)-2*H*-1-benzopyran-6-yl (2*E*,4*E*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexene-1-yl)-2,4,6,8-nontetraenoate), 8)

Tocoretinate (**8**) is a unique α-tocopherol ester of ATRA and has been safely used in Japan for the treatment of decubitus and skin ulcer, acting *via* stimulation of the proliferation of human skin fibroblast [84,85]. The agent is characterized as an RAR antagonist, protein synthesis antagonist, and microbial collagenase antagonist. Unex-pectedly, although tocoretinate is an α-tocopherol ester of ATRA, it was reported to be stable *in vitro* and *in vivo* [86]. This characteristic of tocoretinate has support from observations that tocoretinate enhances the growth of human skin fibroblasts and stimulates the formation of granulation tissue in ulcers, effects that are different from those of either ATRA or α-tocopherol [86]. Furthermore, toxicity tests in animal models have shown that tocoretinate is at least 150 times less toxic than ATRA [87-89]. Tocoretinate is actively being investigated for the possible treatment and chemoprevention of leukemia [90-92].

Liarozole (9, Liazal™)

Following extensive studies by researchers at Janssen Research Foundation (now called Johnson and Johnson Pharmaceutical Research and Development) liarozole (**9**) was identified as a modest inhibitor (IC_{50} = 2.2 – 6.0 μM) of ATRA-4-hydroxylase (CYP26) [93, 94-100]. On the other hand, the compound was shown to be a good inhibitor of rat CYP17 (IC_{50} = 260 nM) and a potent inhibitor of CYP19 [97]. Although liarozole has undergone phase III clinical trials for the treatments of patients with metastatic prostate cancer [101] and also phase II trials for the treatment of ER negative metastatic breast cancer patients [102], its development for these indications have been discontinued [102,103].

Inappropriate metabolism of ATRA could generate a condition of retinoid deficiency, which is characterized by hyperkeratinization and desquamation as seen in acne, psoriasis, and ichthyosis [104]. Because of these reasons, liarozole has also been extensively investigated as a potential agent for the treatment of dermatological diseases [96,105, 106]. Studies in mice revealed that liarozole is able to mimic the antikeratinizing effects of ATRA [96]. In open clinical studies, liarozole was found to be therapeutically effective in patients with psoriasis [107,108] and with ichthyosis [108]. A double-blind, randomized clinical study involving 20 patients with severe plaque-type psoriasis was conducted; half of the patients were treated with oral liarozole (75 mg, twice daily) and the other half were treated with oral acitretin (25 mg/day) [105]. After 12 weeks of treatment, both groups responded with a similar decrease in the PASI (psoriasis area severity index) score from ~20 to ~10. It is gratifying to state that liarozole was recently (2004) approved in Europe and USA as an orphan drug for the treatment of congenital ichthyosis [109,110]. Finally, in a most recent (2005) paper, Lucker and co-workers reported that topical liarozole was effective in the treatment of ichthyosis [110].

***N*-(4-hydroxyphenyl)retinamide (4-HPR, Fenretinide, 10)**

The synthetic *N*-(4-hydroxyphenyl)retinamide (4-HPR, **10**) was first synthesized in the USA by Sporn and colleagues 27 years ago [111]. Although 4-HPR is derived from the natural ATRA, it is less toxic and substantially less tetratogenic [111,112]. 4-HPR is considered to be a non-classical or atypical retinoid, because its biological effects have been shown to act through both retinoid receptor-dependent and –independent mechanisms [reviewed in 113, 114]. Unlike classical retinoids that often induce differenttiation, 4-HPR elicits distinct biological effects, such as generation of reactive oxygen species (ROS) and the promotion of apoptosis. This property has led to suggestions that 4-HPR may exert greater therapeutic activity than a classical retinoid [113,114]. As a result of several promising *in vitro* and *in vivo* studies in a wide variety of tumor cells [3,114], clinical testing of the effectiveness of 4-HPR against neuroblastoma, breast, prostate, ovarian and bladder cancers has been conducted, with modest outcomes. In a large phase II study of Italian women (2,972) aged 30-70 years with surgically removed Stage 1 breast cancer or ductal carcinoma

in situ, oral 4-HPR (200 mg/day) caused no difference in the incidence of breast cancer 7 years after treatment compared to untreated patients [115]. However, there was a beneficial trend (35% reduction of contralateral breast cancer) in premenopausal women and no effect in postmenopausal patients. Phase III trials of 4-HPR as a chemopreventive agent for breast cancer are currently in progress in the USA, and alone in Phase I trials for prostate cancer [6]. Recent reviews on the potential of 4-HPR as a cancer preventive agent should be consulted [116,117].

DEVELOPMENT OF NEW RETINOIDS AND THE FUTURE FOR RETINOID-BASED THERAPIES

Most of the retinoids that are currently in clinical use are RAR or RXR agonists/antagonist. However, in the desire to generate new retinoids/rexinoids that may exhibit fewer side-effects, the goal of chemists and biologist is to develop RAR- and RXR-specific ligands. The generation of these agents has been made possible by recent progress in crystallographic studies on nuclear receptor ligand binding domains that has enabled useful information of ligand-receptor interactions at the molecular level [118]. Thus, various ligands have been developed by computer-assisted procedures using virtual libraries and/or molecular databases. Studies in this area have recently been reviewed by Kagechika and Shudo [8] and will not be discussed further in this review.

Recent developments in the understanding of gene regulation by nuclear receptors and chromatin organization have increased interest among researchers in the cancer field in the identification of agents that modulate gene expression through chromatin re-organization. Retinoids fit the profile of these agents since they can induce, for example, the expression of a number of tumor/growth suppressor genes, which otherwise are transcriptionally silent in cancer cells. A number of tumor/growth suppressor genes such as RARβ, TIG1, etc, are epigenetically silenced because of DNA hypermethylation in their promoter regions [119,120]. As loss of RARβ has been linked to retinoid resistance, and RARβ is a tumor suppressor as well as an intracellular effector of retinoid action, a therapy involving a combination of retinoids and histone deacetylase and/or histone methy-transferase inhibitors may show synergistic efficacy in cancers. As a proof of concept, reversal of transcriptional silencing of RARβ gene and increased growth inhibition has been observed, in the treatment of t(15;17) ATRA-resistant patient with a combination of the HDACi sodium butyrate and ATRA [121]. In addition to HDAC inhibition, reversal of DNA hypermethylation by demethylating agents, 5-aza-2'-deoxycytidine has been shown to restore ATRA-mediated differentiation/growth inhibition in many head and neck squamous cell carcinomas [120]. In addition, there are several studies that document synergistic efficacy in some leukemia and solid tumor cells *in vitro* and *in vivo* [2, 122, 123].

As stated earlier, RXR is a promiscuous dimerization partner for several nuclear receptors, including those related to lipid physiology, such as PPARs, LXRs, and FXRs [124]. Since RXR selective ligands (agonists, also called rexinoids) can elicit similar activities to ligands of the heterodimer partner receptors, it is believed that these agents may be useful as anti-diabetic and anti-obesity agents [125].

CONCLUSION

There is now compelling evidence from the number of retinoids in the clinic and in clinical studies (Table **1**) that these molecules exhibit efficacy in human diseases. The use of ATRA for the treatment of acute promyelocytic leukemia is considered a successful therapy in our view. It is the hope that the application of retinoids, most probably more receptor specific retinoids/rexinoids, in combination with other chemotherapeutic agents, will lead to broad clinical utility in many diseases. We anticipate that the retinoid field will continue to expand as researchers gain more information about new levels of retinoid/rexinoid biology and their relevance to human diseases.

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