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ANTIANDROGENS: CLINICAL APPLICATIONS

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Summary—Antiandrogens, preventing androgen action at target tissue level, are used in the treatment of various androgen-dependent diseases. Pharmacologically these substances have either a steroidal structure, like cyproterone acetate (CPA) and spironolactone (SPL), or a non-steroidal structure, like flutamide (FLU). In women with hyperandrogenism (PCO syndrome, idiopathic hirsutism, acne), clinical benefit may be obtained with CPA, which also displays a progestational activity and an antigonadotropic effect. CPA (25–50 mg/day) is used in combination with ethinyl-estradiol (EE) (20–30 μg/day) in reversed sequential regimen. SPL, less effective than CPA, may be employed in moderate hirsutism and acne at dosages of 100–200 mg/day. During SPL treatment menstrual irregularities are frequent: in this case an association with oral contraceptives is indicated. SPL + bromocriptine (2.5–5 mg/day) has been experienced with success in PCO syndrome. The pure antiandrogen FLU, inducing progressive increase in LH and testosterone secretion, may be used only in combination with oral contraceptives. In men antiandrogens have been tested in BPH and prostatic carcinoma. In BPH the decrease in nuclear receptors and DHT nuclear content during CPA or FLU may represent the rational base of the medical treatment. An improvement in urinary obstructive manifestation has been observed with CPA alone or associated with tamoxifen (100 mg + 100 mg/day). In advanced prostatic carcinoma antiandrogens represent a good alternative to estrogen therapy with less side effects and in combination with surgical or medical castration (LH–RH analogues) achieve a complete androgen blockade. An increase in the percentage of remissions and survival has been reported.

INTRODUCTION

According to Dorfman [1], "antiandrogens are substances which prevent androgens from expressing their activity at target sites". They compete with dihydrotestosterone for the specific receptor; the antiandrogen–receptor complex inhibits the androgen-mediated processes and the protein synthesis.

In this respect weak agonists, which compete less than endogenous hormones and dissociate rapidly from the androgen receptor, must be kept separate from potent agonists, which form a complex with the receptor molecule and dissociate slowly [2]. Antagonists of endogenous androgens are therefore the weak agonists, which rapidly dissociate from the receptor and need only a continuous supply of the compound in order to achieve full inhibition of the endogenous and even of exogenously administered androgens [3].

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The potency of agonist and antagonist compounds can be evaluated by means of different procedures.

The most reliable pharmacological assays used for the estimation of the antiandrogenic activity are those based on the measurement of the relative binding affinity (RBA) [4]. Previous assays based on the weight of rat sex accessory tissues, replaced by the more sensitive determination of [^{3}H]thymidine incorporation (which reflects the rate of DNA synthesis) [5], have actually been overcome by new *in vitro* techniques based on the interaction of antiandrogens with androgen receptors and on the estimation of RBA either in rat prostatic cytosol [6] or in dispersed human genital skin fibroblasts [7]. These assays established that spironolactone has an ability to compete for androgen receptors greater than cyproterone acetate and flutamide [7].

These *in vitro* techniques, however, cannot discriminate those compounds which require transformation into more or less potent congeners responsible for the favourable clinical effects. Furthermore, the RBA method does not discriminate the agonists from all class of antagonists, as it can be obtained with an

in vitro, rapid, quantitative system, sensitive enough to accurately measure the antiandrogenic activity (e.g. LH response to LH-RH of rat pituitary cells in primary culture [8], induction of specific protein in androgen-dependent human cell lines [9] and introduction of steroid receptor gene into eucariotic cells [10]). Of course, only *in vivo* biological assays in animal models allow the study of active metabolites of antiandrogens.

The antiandrogens so far developed include compounds with steroidal structure, such as cyproterone acetate (CPA) and megestrol acetate, displaying also progestational and antigonadotropic effects, or spironolactone (SPL), and compounds without steroidal structure, such as flutamide (FLU) and nilutamide, which are considered pure antiandrogens (Fig. 1). The latter substances, acting also at the hypothalamic–pituitary level, inhibit the negative feedback of the gonadal steroids, so that more gonadotropins are released by the hypophysis and more testosterone and estradiol by the gonads.

Pure antiandrogens, therefore, cannot be used alone, but must be employed in combination with compounds which inhibit gonadotropin secretion, whereas steroidal antiandrogens at high dosage are able to block gonadotropin and androgen secretion. Spironolactone competes for androgen receptor binding and inhibits testosterone biosynthesis by decreasing the microsomal cytochrome *P*450-dependent enzymes.

CPA may be administered orally at dosages of 50–200 mg/day or intramuscularly in the depot form, 300 mg every 7 days: it is rapidly adsorbed, reaching maximal plasma levels in a few hours. Half-life is 1.5 ± 0.6 days. Excretion occurs 30% via the urine and 58% via the bile, and is almost completed by two days after an oral dose. An equilibrium between administration and elimination is obtained after 5–8 days of treatment [11].

FLU, as shown in studies performed in experimental animals, after an oral dose, is rapidly adsorbed, reaching the maximal levels in plasma after 4–6 h. Excretion occurs 95% via the kidney and 5% via the bile, being almost completed by 3 days after an oral dose. Half-life is 45–50 min after an intravenous dose in the monkey, whilst after an oral administration it is rapidly metabolized in animals and in men, mainly by hydroxylation of the side-chain to hydroxy-flutamide. Tissue distribution studies, in fact, have shown that flutamide is low in all tissues, whilst hydroxy-flutamide is present in concentrations up to 70 times the flutamide content in target organs, such as rat ventral prostate and seminal vesicles, where it not only acts by inhibiting tissue uptake and retention of testosterone, but also inhibiting the formation of the nuclear steroid–receptor complex [12].

SPL, administered orally, is rapidly adsorbed and maximal plasma levels are reached within 30–60 min: then it starts to decline by the 12th hr with a monoexponential curve between the 35th and 96th hr after dosing. The excretion occurs with urine and feces, the biliary route being essentially related to the elimination of the metabolites formed [13]. SPL, in fact, is mainly metabolized to canrenone and potassium canrenoate after an oral dose. In this respect it is important to note that SPL is a strong competitor for androgen receptors and therefore a potent agonist, whilst canrenone is a weak competitor [7]. Therefore the antagonist action of spironolactone, beside its effect on cytochrome *P*450, may also be due to the formation of canrenone, which dissociates rapidly from the receptor complex, but completely inhibits endogenous androgens when a continuous supply of the compound is maintained.

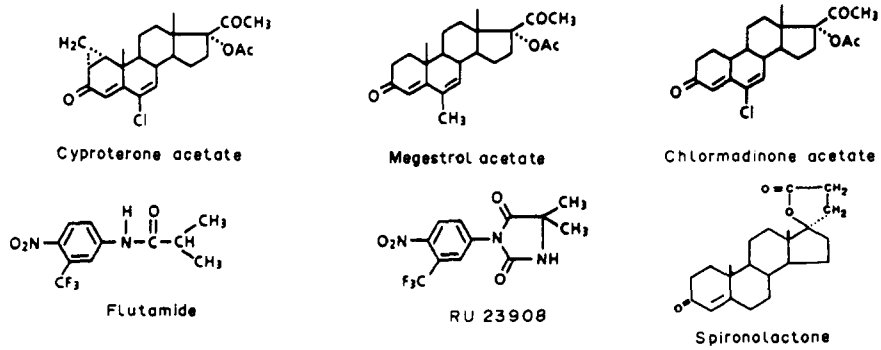

Fig. 1. Chemical structure of some steroid and non-steroid antiandrogens.

Antiandrogens may be employed in the treatment of female hyperandrogenic states, such as hirsutism, acne and seborrhea, prostatic diseases, such as benign prostatic hyperplasia and advanced prostatic carcinoma, precocious puberty, hypersexuality and sexual deviations. This report deals with our experience with the clinical use of CPA, FLU and SPL in these disorders.

HIRSUTISM

Many investigators have referred to the efficacy of CPA in 70–80% of the women with signs of hyperandrogenism [14–22]. Addition of estrogens is necessary to avoid the risk of conception of a feminized fetus, to ensure regular menses, to increase SHBG levels, and to reinforce the antigonadotropic action of CPA.

The depot effect of this compound, which is stored in adipose tissue during the period of administration in the follicular phase, provides a reverse sequential regimen proposed by Hammerstein and Cupceancu [14]: CPA is administered for 10 days (5th–14th day of the menstrual cycle) at the dosage of 50–100 mg/day, whilst ethynil-estradiol is given for 20 days (5th–24th day of the menstrual cycle). Estradiol dissolved in alcoholic excipient may be also administered percutaneously [20]: skin penetration is around 10%, which provides physiological estrogen levels sufficient to ensure regular bleeding, avoiding the risk of the hepatic toxic effects of the oral administration.

After 3 months' treatment plasma androgens decrease significantly, reaching the normal range after 6 months, and the Ferriman and Gallway reference score for hirsutism [23] is reduced by 50% with respect to the basal score. The normalization of plasma 3α-androstanediol, marker of the peripheral androgen utilization [24], confirms the efficacy of CPA treatment, which may be decreased to the maintaining dosage of 25–50 mg/day [25].

Side effects, such as nausea, headache, astenia and in 9% of the cases loss of libido are very rare using the percutaneous route for estrogens.

Figure 2 reports our results obtained in 20 cases of idiopathic hirsutism, aged 18–24 yr, 11 with normal menstrual cycles and 9 with

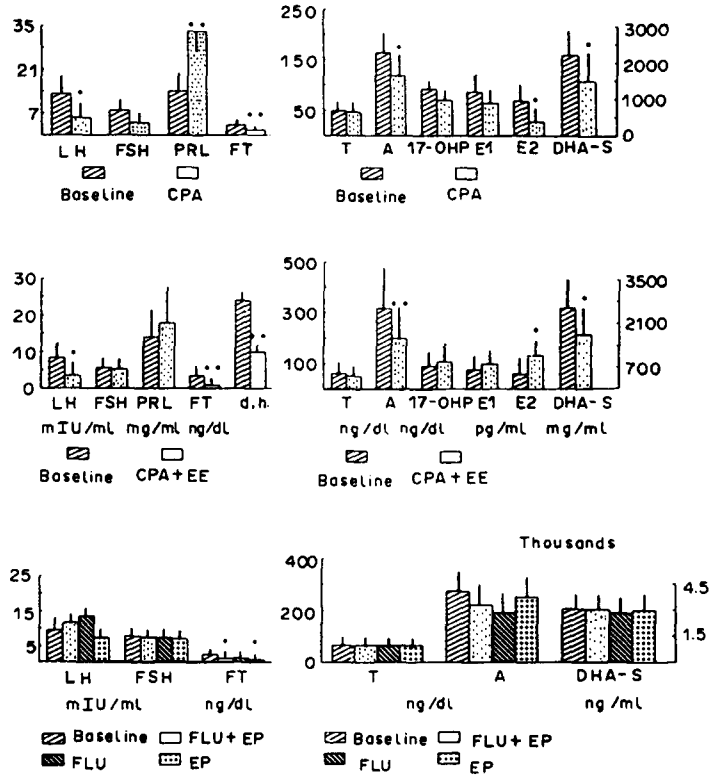

Fig. 2. Idiopathic hirsutism: hormonal pattern in baseline condition and after treatment with cyproterone acetate (CPA) alone or in association with ethynyl estradiol (EE), and after flutamide (FLU) alone or in combination with estroprogestin (EP), and after EP alone. Gonadotropins: LH; FSH; prolactin: PRL; free testosterone: FT; degree of hirsutism: d.h.; testosterone: T; androstenedione: A; 17α-hydroxyprogesterone: 17-OHP; estrone: E1; estradiol: E2; dehydroepiandrosterone-sulphate: DHA-S (see the scale on the right side).

oligomenorrhea. Mean values of Ferriman and Gallway score were 24 ± 2. Pre-treatment hormonal pattern was characterized by high levels of plasma androstenedione and free testosterone: under CPA treatment (50 mg/day CPA + ethynil-estradiol 20 μg/day) both the androgens fall to normal concentrations and after 6 months mean hirsutism score decreased to 12 ± 2. So far, more than 250 cases have been treated according to this protocol, positive response being recorded in 80% of the patients. When hirsutism is moderate, a lower dosage of CPA may be utilized (2 mg CPA + 35 μg ethynil-estradiol for 21 days) with satisfactory results [26].

As an alternative, SPL may be used at dosages of 100–200 mg/day continuously or in cyclic regimen [21, 26–31]. The efficacy of lower doses (50–75 mg/day) [32] is controversial. After 3 months of treatment with a high dosage of SPL (300 mg/day), plasma testosterone decreases significantly, whilst estrogens and progesterone levels rise: gonadotropin FSH-LH show an irregular anovulatory pattern, which may be responsible for menstrual irregularities. In this case addition of oral contraceptives is required to ensure regular menses. At a daily dose of 100 mg slight, non-significant modifications of circulating androgens are observed: at this regimen, therefore, the positive clinical effects of SPL are only due to the competitive action at receptor level.

Excellent results may be obtained combining the antiandrogenic action of SPL to bromocriptine (Br), which reduces LH secretion, increasing at hypothalamic level the inhibitory dopaminergic tone on GnRH release or acting at pituitary level by reducing the gonadotroph sensitivity to GnRH, regardless from high or normal values of prolactin [33, 34].

We have experimented with the combination therapy, SPL (100 mg/day) plus Br (2.5 mg/day) for 20 days every month, in 21 cases of polycystic ovary syndrome (PCO), aged 19–43 yr, presenting a mean hirsutism score of 26 ± 2, 17 with oligomenorrhea and 4 with amenorrhea. The hormonal pattern was characterized by a high LH/FSH ratio (>3) and increased plasma levels of androstenedione and testosterone; prolactin levels were at the upper limit of the normal range. After 6 months of therapy, a normalization of LH/FSH ratio, a significant decrease in prolactin, androstenedione and testosterone levels, and an increase in plasma estradiol were observed. These important biochemical modifications were associated with a marked reduction of mean hirsutism score (14 ± 2) within 5–6 months, and after 10–12 months of treatment restoration of normal menstrual cycles was registered in 15 cases. Ultrasonography revealed reduction of the ovarian size and of degree of cystic degeneration. In the second half of the cycle progesterone levels reached values of 11 ± 1 ng/ml. The hormonal and clinical response was also maintained during the 6 months following therapy withdrawal.

The reported effects by means of the combined treatment with SPL and Br in PCO patients are mainly due to Br. In 1984 Falaschi *et al.* [35] reported that responders to bromocriptine alone at dosages of 5–7.5 mg/day are 90% of the cases of polycystic ovary syndrome with high prolactin levels and 50% of the cases with normal prolactin. Our results with the combined therapy, therefore, effective in 70% of the normoprolactinemic PCO patients, suggest that SPL, by inhibiting the androgen utilization at the peripheral and the hypothalamic level, may potentiate the modulatory role of the lowest dosage (2.5 mg/day) of Br, normalizing the pulsatile secretion of GnRH (Fig. 3).

Up to now only one report in the literature deals with the utilization of a pure antiandrogen in hirsutism. Cusan and Dupont [36] in 1989 referred to the clinical and hormonal effects of FLU in combination with an oral contraceptive in 18 women affected by idiopathic

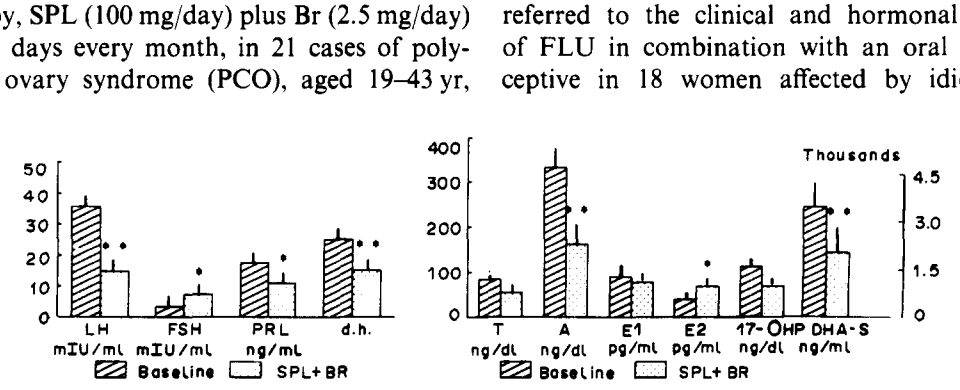

Fig. 3. Polycystic ovary syndrome: hormonal pattern in baseline condition and after treatment with bromocriptine (BR) associated with spironolactone (SPL). For abbreviations see Fig. 2.

hirsutism, treatment being highly effective and well tolerated.

Our experience deals with the use of FLU (250 mg twice a day) associated with an oral contraceptive devoid of androgenic effects (gestodene 75 μg + ethynil-estradiol 30 μg/day for 21 days) in 11 women affected by idiopathic hirsutism, aged 18–27 yr, showing a mean hirsutism score of 22 ± 3, 7 with oligomenorrhea and 4 with normal cycles. As for CPA, the association with estroprogestin compounds is recommended to avoid the risk of pregnancy and to inhibit the gonadotropin rise. In 7 cases, only gestodene + ethynil-estradiol was administered for 3 months and in 5, FLU only for 3 months.

Pre-treatment hormonal values were characterized by high levels of androstenedione and free testosterone. During the combination therapy plasma androstenedione was not affected, whilst free testosterone was significantly reduced, probably on account of the estrogenic component of the oral contraceptive, which increases SHBG concentrations: in fact a parallel decrease in free testosterone was also found when only the estro-progestin compound was administered, but not with FLU alone (Fig. 2). This could explain the best clinical results obtained with the combination therapy, FLU plus oral contraceptive, after 5–6 months in all cases, mean hirsutism score being decreased to 11 ± 1. Using the oral contraceptive alone, hirsutism was slightly reduced to mean values of 18 ± 3. Treatment was well tolerated, only 3 patients complained of nausea and gastralgia after 3–4 months of therapy: also in these cases liver and kidney function tests and other hematological parameters were normal. Dry skin was referred by 6 patients, in analogy with Cusan and Dupont's report [36]. This combined treatment, therefore, carried out with low doses of FLU (500 mg/day), may represent an effective alternative to CPA in idiopathic hirsutism, since it inhibits hair-growth, without important side effects, at least during the 6 months of follow-up.

The Canadian group [36], who treated 20 hirsute women with 500 mg/day of FLU associated to norethindrone and ethynil-estradiol for 12 months, referred to dry skin only, in 70% of the cases, the biochemical parameters being always normal. A longer follow-up is however necessary before concluding that this drug may be safely used in young healthy women. Reduction of hirsutism was obtained by Cusan and Dupont [36] not only in idiopathic hirsutism but also in 8 cases affected by PCO syndrome.

Recurrence of hirsutism after the withdrawal of the antiandrogen therapy is frequent with an inverse relationship with the duration of treatment.

ACNE AND SEBORRHEA

Genetic predisposition, hyperkeratinization of the follicular infundibulum, colonization of micro-organisms, immunological reactions, sebum secretion and androgen activity are pathogenetic factors involved in the development of acne. Androgen activity may be expressed either by an overproduction of these steroids or by their increased utilization at the level of acini and ducts of sebaceous glands, as a consequence of low levels of SHBG or increased 5α-reductase [37, 38]: androgens raise the mitotic activity inducing seborrhea and promoting epithelial proliferation.

Antiandrogens, therefore, may also be properly used in the treatment of these skin disorders. Excellent results are, in fact, obtained with low doses of CPA (2 mg/day) combined with ethynyl-estradiol (35 μg/day). Seborrhea improves first, but after the third month of therapy acne also regresses in more than 80% of the case, mainly in those with papulo-pustulous lesions and premenstrual exacerbation. In many patients the success achieved is maintained for many months after withdrawing the treatment. In resistant cases and when hirsutism is associated, low doses of CPA (25–50 mg/day) and ethynyl-estradiol (20 μg/day) may be administered with satisfactory results in the majority of the patients [39, 40]. As an alternative regimen, spironolactone may be used at the dosage of 100 mg/day for 20 days [41]. The maximal clinical effect is obtained in 80% of the cases after the second trimester of treatment. Side effects are represented by menstrual irregularities that in most cases regress after the second–third month of therapy.

Our experience deals with the treatment of androgenic acne with spironolactone (100 mg/day for 20 days every month) in 18 cases, showing normal androgen plasma levels. Excellent results, with regression of skin lesions, were observed in all cases after 4–6 months of therapy which was continued for 8–12 months. Relapse occurred in 40% of the cases 6–12 months after the treatment was interrupted.

BENIGN PROSTATIC HYPERPLASIA (BPH)

The hormonal imbalance plays an important role among the genetic-, dietary- and age-related ethiologic factors of BPH [42–49].

The relationship between the prostate and the testis has been widely investigated, and in 1944 Moore [50] demonstrated that the prostate decreases in castrated men and does not develop in cases of severe hypogonadism and testicular feminization due to deficient 5α-reductase, whilst in patients with testicular feminization due to absence of androgen receptors prostatic hyperplasia is never found [51].

DHT plays an important role in prostatic growth: this active metabolite, in fact, accumulates in androgen target tissue and its concentration in BPH tissue is slightly higher than that found in the normal prostate: moreover it represents 90% of the nuclear steroids [44, 52–55].

There is also strong evidence that estradiol plays an important role in the pathogenesis of BPH: high concentrations of estradiol and estrogen receptors, in fact, are found in the stromal compartment and mainly in the stromal nuclei [56–58].

A further demonstration of the endocrine ethiology of this disorder are the effects of the androgen suppression obtained with medical castration by means of GnRH analogues, or the use of antiandrogens and inhibitors of 5α-reductase. These approaches are particularly suitable in patients with low–middle grade symptoms of urinary obstruction and in those who refuse, wish to postpone, or cannot face surgery [59–69].

Geller *et al.* [61] have shown in a double-blind randomized study that megestrol acetate (120 mg/day) induces a significant reduction in tissue DHT concentrations with a marked improvement of the urinary obstructive symptoms (maximum/mean flow rates, nicturia, urgency, frequency, hesitancy and dribbling) in 78% of the patients, 6 weeks after the start of the treatment. CPA (50 mg/day) gives similar results [59], whereas FLU shows various degrees of efficacy. In a group of 30 patients treated by Caine *et al.* [66] with FLU at a dosage of 300 mg/day or with placebo for 12 weeks, residual urine and prostate size were not different between the two groups. Similar results were obtained by Bonard *et al.* [67] in 32 BPH patients. More recently a multicenter randomized double-blind study was performed by Stone [68] in 84 BPH patients: after 24 weeks of treatment with FLU 750 mg/day a 41% median decrease in prostatic volume and a 46% increase in full-bladder uroflow was found. The therapy was well tolerated and only 11% of the cases presented side effects, such as breast pain or diarrhea; no changes in libido were noted.

Antiestrogens have also been used experimentally in BPH patients: they are able to decrease the androgen receptors in the nuclei of prostatic tissue and protein synthesis [61, 65, 70] but the clinical results were disappointing, probably on account of their stimulatory effect on gonadotropin and testosterone secretion: Tunn *et al.* [70] have in fact demonstrated that tamoxifen (TAM), at a dosage of 80 mg/day for 6 months, increases the smooth muscle cell compartment with negative clinical results.

On the contrary, testolactone, an aromatase inhibitor, at a dosage of 200 mg/day, decreases by 26% the initial prostatic volume with a marked improvement of obstructive urinary symptoms in half of the patients [61].

The stroma–epithelium interactions and the androgen–estrogen relationship in prostatic growth are the rationale of the combined use of antiandrogens and antiestrogens in the medical treatment of BPH.

Tenaglia and Di Silverio [71] carried out a randomized trial in 166 BPH patients aged 61–73 yr, with the aim to compare the clinical response to CPA alone (50 mg/day) or in combination with TAM (20 mg/day). After 2 months of treatment the most remarkable clinical response was observed in the CPA plus TAM-treated group, who showed a 40–70% reduction of nicturia in 60% of the patients, 30–70% reduction of day-time frequency in 65% and 25–60% reduction of post-minctional residue in 65%. Prostatic volume, evaluated by rectal ultrasonography, was found slightly decreased by 20–25% in 55% of the cases. During treatment 78% of the patients complained loss of libido and reduction of sexual performance. No other side effects were recorded.

Hormonal investigations were carried out by Petrangeli *et al.* [72] in plasma and prostatic tissue of 34 BPH cases, 10 untreated, 9 treated with CPA plus TAM, 6 with CPA alone and 9 with FLU alone (750 mg/day). During treatment with CPA and with CPA plus TAM, plasma testosterone, DHT and 3α-androstanediol decreased significantly, whilst during FLU a rise in plasma testosterone, secondary to the LH increase, and a fall in 3α-androstanediol was observed. In prostatic tissue specimens,

obtained by surgery through transvesical resection, the combination therapy induced a fall of DHT concentrations to the lowest values, probably on account of a decreased 5α-reductase activity due to the inhibition of the estrogen action, whilst all treatments induced a significant reduction of 3α-androstanediol levels, confirming the lack of androgen utilization by the target organ (Fig. 4).

Moreover treatment with CPA plus TAM led to a detection of cytosol androgen receptor (AR) in 50% of the cases, while nuclear AR were never measurable, like during FLU therapy, which did not modify the incidence of cytosol AR. These results are in agreement with those of Albert *et al.* [73] who found that TAM is able to induce a significant reduction of nuclear AR and with those of Huang *et al.* [74] who demonstrated that CPA is able to decrease nuclear AR, on account of a block of the nuclear translocation of AR.

Evidently the combination therapy CPA plus TAM potentiates the negative effect of the two compounds in the nuclei of prostatic tissue, acting at receptor level and on 5α-reductase, both in the stroma and in the epithelium.

PROSTATIC CARCINOMA

Hormonal treatment of prostatic carcinoma is based on the demonstration that malignant prostatic cells are target tissues of androgen action. The goal of the therapy is therefore to reduce the androgenic support to prostatic cancer growth by removing the primary source of circulating androgens. This may be achieved by means of orchiectomy, by suppressing the gonadotropin secretion using LH-RH analogues, reducing the circulating androgens with estrogens or blocking the androgens at receptor levels with antiandrogens [75–83].

The clinical results obtained with CPA treatment alone at high dosage (300 mg/day orally or intramuscularly per week using a depot preparation) are almost comparable to those obtained with estrogens. Furthermore CPA is responsible for a marked reduction in side effects, limited to impotence and depression.

In 1966 Scott and Schirmer [84] treated 10 patients affected by prostatic carcinoma with 100 mg/day of CPA as monotherapy obtaining a remission in 7 cases. Similar results were reported by many other investigators [85–88]. Wein and Murphy [86] reported a 64% of objective remission among 55 patients treated with CPA. A multicentric prospective randomized study initiated in Europe in 1977, including 191 patients from 18 centers revealed a marked effect of CPA on local tumor mass with regression in 66.7% of the cases and improvement of obstructive micturition symptoms in 48% of the patients. Under this regimen plasma testosterone dropped from 4.3 to 1.1 ng/ml after 3 months and remained at this level after 6 months [89]. In 1984 the British Prostate Group referred to a randomized controlled clinical trial of 205 patients treated with orchiectomy, diethylstilbestrol (DES) or CPA: no statistical difference in the clinical response between the 3 groups was found [90]. In 1987 Beurton *et al.* [91] demonstrated in 112 cases of prostatic cancer, 3/4 of whom were advanced, that CPA alone has an immediate action as potent as that of estrogens, even if its antigonadotropic effect is less intense than that induced by estrogens and the fall of plasma testosterone less dramatic, but evidently well counterbalanced by a total receptor blockade. Final results of EORTC study 30761 [92] comparing CPA versus medroxyprogesterone acetate (MPA) and DES, showed that patients treated with CPA achieved better results in terms of objective

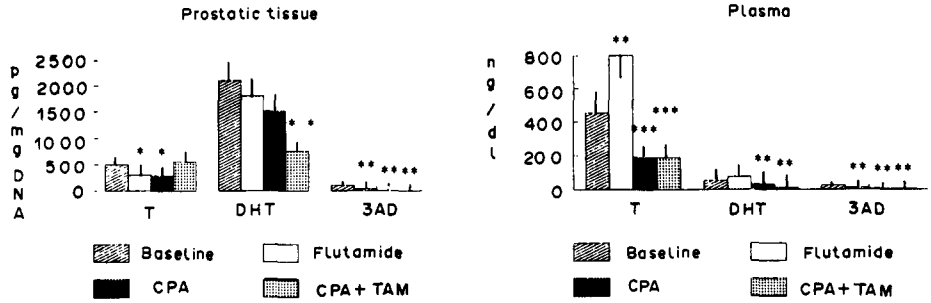

Fig. 4. Benign prostatic hyperplasia: tissue and plasma levels of testosterone (T), dihydrotestosterone (DHT), 3α-androstanediol (3AD) in baseline condition and after treatment with flutamide (FLU), or after cyproterone acetone (CPA) alone or in association with tamoxifen (TAM).

response of local tumor and bone metastases, progression rate, time to progression and survival, than those obtained with the other drugs.

Encouraging results are also obtained with FLU alone or better still with its major metabolite, the hydroxy form, which are as effective as DES with 50% remission rate [93–96]. In 1984 Sogani *et al.* [93] referred to the results obtained in 74 patients treated with 750 mg/day of FLU: clinical improvement was demonstrated in 88% of the cases by the reduction of the primary tumor size and of metastases in bone and soft tissue, regression of bone pain and hydronephrosis, amelioration of general conditions and a significant decrease in serum acid phosphatase. Published the same year is the report of Neri and Kassem [94], concerning the results of a randomized double blind trial performed in 12 institutions, using three regimens: FLU 1500 ng/day; FLU 750 ng/day; DES 1 mg/day. No differences were obtained between the 3 groups as far as the quality and duration of the clinical response and survival rate is concerned. Incidence of side effects, however, were higher in the DES-treated group (cardiovascular complications and gynecomastia) than in the FLU group.

In 1987 Daricello *et al.* [95] reported complete/partial regression in 36% of the patients treated with FLU 750 mg/day and stabilization of the disease in 18% of the cases. Finally in 1989 Prout *et al.* [96] reported a mean survival of 50 months in 50% of the patients who responded to FLU therapy (750 mg/day) and of 17.2 months in 25% of the patients who failed to respond and in 25% who had a subjective response.

Monotherapy with FLU, devoid of important side effects, is therefore valuable in advanced prostatic cancer, even if the modifications of plasma androgen levels are not as consistent as those obtained with CPA. This pure antiandrogen, therefore, although unable to produce a complete androgen inhibition, produces its clinical effects by blocking the nuclear androgen receptors.

A new approach to the treatment of prostatic cancer is achieved using LH-RH analogues, which allow to obtain a medical castration through the block of the gonadotropin secretion and then the inhibition of the testicular androgen production [82, 83].

In 1982 the concept of total androgen blockade was introduced to the endocrine therapy of prostatic cancer [97]. It has been, in fact, hypothesized that prostatic carcinoma contains androgen-hypersensitive cells, which may be stimulated by the 40% intraprostatic DHT presumably formed by the conversion of adrenal androgens, following the suppression of the testicular secretion. A total suppression of both the testicular and adrenal androgens achieved by means of surgical or medical castration with LH-RH analogues plus antiandrogens, may be therefore more effective than monotherapy in inhibiting prostatic cells growth [98, 99].

This theory is supported by the fact that hypophysectomy, adrenalectomy or treatment with aminoglutethimide or ketoconazole provide a further period of remission in many patients in relapse after orchiectomy of estrogen therapy, reducing the adrenal androgen secretion and then the intraprostatic DHT concentrations by 95%. Moreover when LH-RH analogues are used for medical castration, the concomitant treatment with steroidal antiandrogen prevents the initial rise in gonadotropin LH and testosterone, which may be responsible for a disease flare-up [100–103].

The pioneer study on the treatment of advanced prostatic cancer with a combined endocrine therapy (orchiectomy associated to CPA 200 mg/day) was reported by Bracci and Di Silverio [104] in 1979 in previously untreated patients: a survival rate at 5 yr higher than that obtained with estrogens was demonstrated. Furthermore in the 237 patients with stage C–D prostatic carcinoma they reported a survival rate of 66% after 36 months and 58% after 72 months, declining to 54 and 35% respectively when only stage D was considered. In 1980 Giuliani *et al.* [105] reported similar results, the survival rate at 4 yr being 70% in stage C and 20% in stage D prostatic carcinoma.

The best clinical response to the combination therapy using orchiectomy or LH-RH analogues associated to FLU or nilutamide is that reported by Labrie *et al.* [99] who achieved a positive objective response, according to the criteria of the National Prostatic Cancer Project, in almost all patients, relapse occurring in only 5 cases out of 118 patients after 24 months of treatment and death in only 1 case after 9 months.

According to the EORTC study 30805 of Robinson [106], on the contrary, orchiectomy with CPA does not appear to give superior results to those of orchiectomy alone, considering the time to progression and the length of survival. Similar results were obtained

in randomized double studies of several investigators [107–109].

However with the combination therapy a more frequent improvement in bone pain and in performance status, a greater decrease in tumor masses and more frequent normalization of prostatic acid phosphatase may be obtained in many cases [110].

In the study of Namer *et al.* [111] 96 patients were orchiectomized and randomly assigned on a double-blind basis to a placebo (53 cases) or to a nilutamide group (43 cases): the best objective clinical response was obtained in 49% of group 1 and in 66% of group 2, but the difference between the rates of improvement in bone pain, performance status, obstructive symptoms and actuarial survival rates between the two groups were not significant. Becker and Klosterhalfen [112], in a randomized trial carried out in 78 patients with metastatic cancer treated with estrogens or prednisolone or CPA or placebo after orchiectomy, found parallel remission curves, without significant differences between the 4 groups.

In 1984 the US National Cancer Institute sponsored a randomized controlled multicenter intergroup study to evaluate the efficacy of the combined therapy. The double-blind trial included 617 previously untreated stage D2 prostate cancer patients, 603 being evaluable for the response. In the monotherapy group, 301 patients received leuprolide (1 mg/q day s.c.) with placebo and in the combined treated group, 302 leuprolide with FLU (250 mg/q 8 h p.o.). Results published in 1989 revealed the best clinical response in leuprolide plus FLU group, median time to progression being 16.5 months and median survival time 35.6 months, whereas with monotherapy median time to progression was 13.6 months and median survival time 28.3 months. Furthermore the addition of FLU to leuprolide lessened the severity of the flare effects, reported in 8–32% of the patients treated with leuprolide alone [113].

In 1984 a multicenter randomized trial with a LH-RH analog (Goserelin depot, 6 mg i.m. every 28 days) was started. Up to October 1989, 326 patients with stage D prostatic carcinoma, mean age 71 yr, were recruited: 163 were treated with Goserelin alone and 163 in combination with CPA (200 mg/day).

In Fig. 5 the hormonal response to these treatments are reported and compared to the results obtained using FLU or surgical castration alone or combined with antiandrogens. Plasma gonadotropins FSH-LH were increased after orchiectomy alone or combined with FLU, whilst they were markedly reduced by the LH-RH analogue alone or combined with antiandrogens. Plasma testosterone had fallen to very low levels under all treatments (Fig. 6), whereas the lowest values of androstenedione and dehydroepiandrosterone sulphate were found under CPA combined with surgical or medical castration, on account of the inhibitory effect of this compound on the adrenal androgen secretion.

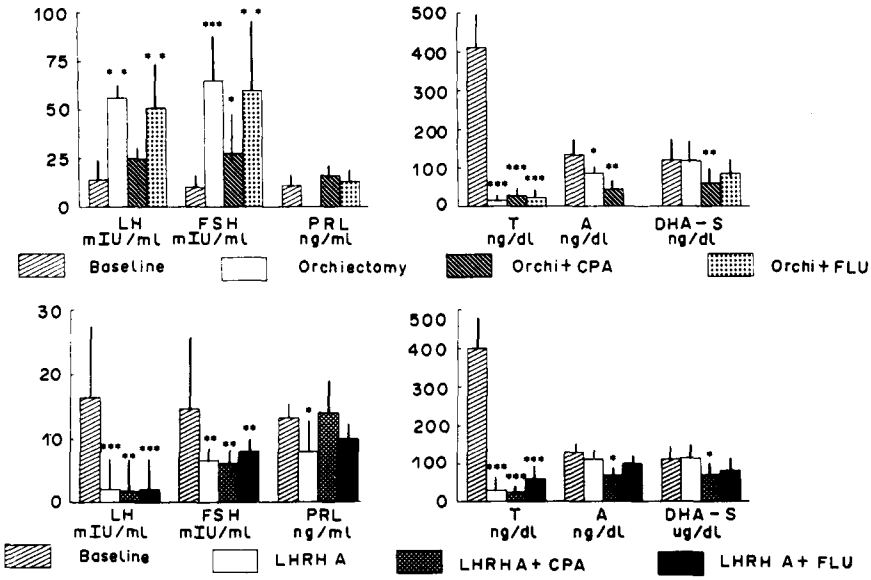

Fig. 5. Prostatic carcinoma: hormonal pattern in baseline condition, after surgical (orchiectomy) or medical (LH-RH A) castration alone or in association with cyproterone acetate (CPA) or flutamide (FLU). For abbreviations see Fig. 2.

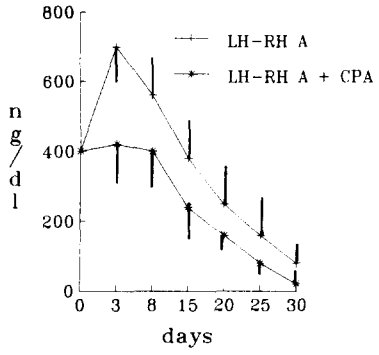

Fig. 6. Prostatic carcinoma: testosterone pattern during the first month of treatment with LH-RH A alone or associated with cyproterone acetate (CPA).

From a clinical point of view, median survival was 130 weeks under treatment with the LH-RH analogue alone and 103 weeks with the combination therapy: this difference, however, was without statistical significance.

In conclusion the question of whether or not to use combined therapy to treat patients with advanced prostatic cancer will still be relevant in future years, and additional controlled trials considering the risks, benefits and costs of chemical castration vs surgical castration in association with antiandrogens need to be further evaluated.

According to Di Silverio *et al.* [114, 115] FLU may be used to treat patients in relapse after medical or surgical castration combined with CPA, since it may add a further period of remission. In this respect 100 patients with stage D prostatic carcinoma in progression were studied: in 48 the treatment with CPA (200 mg/day) was continued, whilst in the remaining 52 cases, after a period of 3 months without antiandrogens, FLU treatment (750 mg/day) was started in combination with a LH-RH analogue (Goserelin depot i.m.), when surgical castration was not performed. The response was positive in 80% of FLU-treated patients: stage D2 patients showed a further period of survival of 6 months, stage D1 patients of more than 12 months. The highest response rate was observed at local level, particularly in the primary prostatic tumor, bone metastases being the main site of progression. The response was also positive in cases of undifferentiated G3 prostatic cancer, probably on account of the antimitotic action of the drug (Fig. 7).

CONCLUSIONS

Efforts have been made in the recent years to obtain compounds able to counteract hormonal action. These studies led to the development of many anti-hormonal substances blocking the androgen, estrogen, progestational, glucocorticoid and mineralocorticoid activity mainly at the receptor level. So far antiestrogens have been widely employed in the treatment of hormone-dependent breast cancer and antiandrogens in the treatment of benign or malignant prostatic tumors. Pharmacological and clinical investigations have also been performed on different pathological conditions favorably treated with antiprogestative, antiglucocorticoid and antimineralocorticoid substances.

The anti-hormonal effects of antiandrogens have been clearly demonstrated both *in vitro* and *in vivo*. On this basis it has been reported that antiandrogens could also be employed in pathological conditions other than androgen-dependent prostatic tumors. The antiandrogen action, in fact, may be useful in the treatment of all the cases related to androgen hyperproduction, such as precocious puberty, female hirsutism and virilism, acne and seborrhea, as well as of other androgen-dependent tumors. In this respect it is worthwhile to note that melanoma and bladder carcinoma are provided with AR and therefore possible candidates to antiandrogenic treatment. However, the best

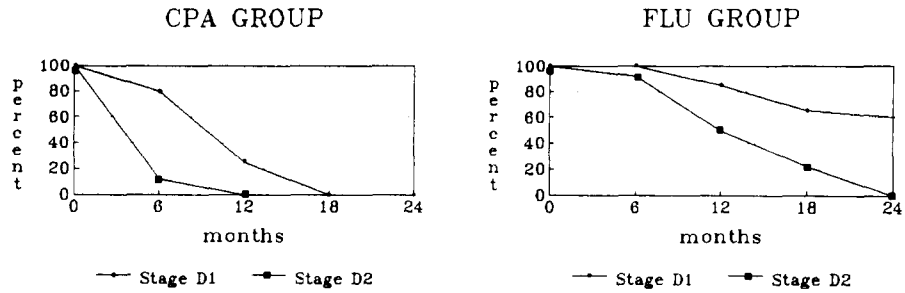

Fig. 7. Survival rate of stage D1 and D2 prostatic carcinoma in relapse after either medical or surgical castration associated with cyproterone acetate (CPA): patients continuing CPA treatment compared to those under flutamide (FLU). (From Di Silverio *et al.* Ref. [115].)

clinical results so far obtained are those in benign and malignant prostatic tumors.

Our experience deals mainly with the clinical use of different antiandrogens in hirsutism, acne and prostatic tumors. Antiandrogens have been chosen in each case according to their main mechanism of action and pharmacodinamic, in order to obtain the best clinical response with the lowest adverse side effects. Clinicians should be advised on the possible use of these tools in different female and male pathological states, but is also desirable that they either refer to already reported clinical trials or use well experimented compounds rather than new substances whose side effects are still not well known.

Perspective will be aimed to synthesize new drugs with more specific antiandrogenic activity and less side effects.

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