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ARIMIDEX™: A New Oral, Once-A-Day Aromatase Inhibitor

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ARIMIDEX® is a potent and selective aromatase inhibitor undergoing evaluation as a treatment for postmenopausal women with advanced breast cancer. Studies examining the pharmacology of ARIMIDEX were conducted in both animals and humans. In animals, ARIMIDEX elicits maximal aromatase suppressive activity at a dose of approx. 0.1 mg/kg, does not alter adrenal steroid hormone biosynthesis, and at a dose of 1 mg/kg, has no other pharmacologic effects other than aromatase inhibition. In this overview, the pharmacodynamic, pharmacokinetic, and safety profiles of single and multiple daily doses of ARIMIDEX are reported in humans. Daily doses of 1–10 mg of ARIMIDEX suppressed estradiol levels to the maximum degree measurable using sensitive estrogen assays. ARIMIDEX had no clinically significant effects on the response of cortisol and aldosterone to ACTH stimulation. Absorption of ARIMIDEX was rapid, with maximum plasma concentrations occurring within 2 h after oral administration. Plasma concentrations of ARIMIDEX rose with increasing doses of the drug. The elimination half-life of ARIMIDEX in humans ranged from 30 to 60 h. Consistent with the long plasma half-life, steady state plasma concentrations were 3–4-fold higher than plasma concentrations observed after single administration of 1, 3, 5, or 10 mg doses. Long term treatment of breast cancer patients with 10 mg/day has continued in 17 patients without an escape of estradiol suppression. Previously, these patients had received on average 2.6 systemic treatments for breast cancer and had significant metastatic disease. Three of the 17 patients continued ARIMIDEX treatment for 20 months and beyond. Given the number of previous treatments and tumor burden at the start of treatment, the response to ARIMIDEX treatment is encouraging. Phase III studies are now underway to assess the efficacy and safety of ARIMIDEX in the treatment of advanced breast cancer.

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INTRODUCTION

Since the benefit of bilateral oophorectomy for the treatment of advanced breast cancer was first described by Beatson in 1896 [1], a variety of pharmacological agents designed to alter the effect of estradiol on breast cancer tissue have been evaluated. NOLVADEX® (tamoxifen citrate), an antiestrogen, is widely used in the management of breast cancer both for adjuvant treatment and for advanced disease because it is so well tolerated [2]. Although the benefits of tamoxifen in the treatment of breast cancer are clearly established [3], a number of women still relapse from their disease and require palliative treatment. Therefore, a treatment that offers a palliative effect with low toxicity is greatly desirable.

Progestins, such as megestrol acetate and medroxyprogesterone acetate, have been used for the treatment of advanced breast cancer following NOLVADEX therapy. Although they have similar efficacy to NOLVADEX, progestins are usually given after relapse or disease progression following NOLVADEX therapy because they are associated with adverse effects such as weight gain and thromboembolic complications [4].

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Aminoglutethimide was the first aromatase inhibitor to be evaluated for the treatment of breast cancer. A review of 28 clinical trials conducted in Europe with different doses of aminoglutethimide given to postmenopausal women with advanced breast cancer showed average overall response rates (complete or partial response) of 19–30% [5]. Patients treated with aminoglutethimide have reported a wide spectrum of adverse events such as drowsiness (33%), rash (23%), nausea (15%), and ataxia (4%) [6]. This, along with the need for concomitant hydrocortisone administration [7], has limited the clinical use of aminoglutethimide.

Another aromatase inhibitor, formestane (4-hydroxyandrostenedione), is available commercially in some European countries; use in uncontrolled trials has shown response rates similar to those reported for aminoglutethimide [8]. Unfortunately, formestane is administered by intramuscular injection every 2 weeks and is associated with injection-site reactions in more than 10% of treated patients [9].

ARIMIDEX® (ZENECA ZD1033), an achiral triazole derivative, is a potent and selective aromatase inhibitor currently being evaluated as a treatment for postmenopausal women with advanced breast cancer. Preliminary data suggest that this compound is extremely potent in lowering circulating estradiol levels; is highly selective for inhibiting the aromatase enzyme complex; and is well tolerated. Once efficacy is established, ARIMIDEX could offer a distinct advantage over the existing hormonal treatments available for postmenopausal women with advanced breast cancer who have failed NOLVADEX treatment. This article summarizes the ARIMIDEX pharmacodynamic, pharmacokinetic, and treatment results in patients with advanced breast cancer patients.

PRECLINICAL PHARMACOLOGY

The preclinical pharmacology of ARIMIDEX has been previously described and is summarized here [10]. *In vitro* ARIMIDEX significantly suppresses the activity of human placental aromatase (IC_{50} of 0.043 μg/ml or 14.6 nM). *In vivo* studies of ovarian aromatase activity in the rat showed that an oral dose of 0.1 mg/kg given on day 2 or 3 of the estrous cycle is sufficient to block ovulation in mature females and androstenedione-stimulated uterine development in prepubertal females. In male pigtailed monkeys, twice-daily, oral administration of 0.1 mg/kg (or greater) of ARIMIDEX reduced circulating estradiol concentrations by 50–60%, as a result of the inhibition of peripheral aromatase activity.

The selectivity of ARIMIDEX was evaluated through a variety of pharmacological methods used to determine its effect on other cytochrome *P*450 enzymes. Based on the monkey data, the margin of selectivity of ARIMIDEX is a least 30-fold and on dog data at least 100-fold with respect to 11-hydroxylase enzyme inhibition. Plasma aldosterone concentrations in male rats are not significantly affected by doses of up to 20 mg/kg of ARIMIDEX. Its margin of selectivity with respect to 18-hydroxylase inhibition is therefore at least 200-fold. By comparison, in rats, fadrozole causes a significant (75%) fall in aldosterone at doses only 2.5–5 times its aromatase inhibitory dose.

ESTROGEN SUPPRESSION WITH ARIMIDEX

Estrogen suppression with single and multiple daily dosing with ARIMIDEX was evaluated in 4 clinical trials. In all of these trials circulating estradiol was measured using a highly sensitive and validated radioimmunoassay with a detection limit of 3.7 pmol/l [11, 12].

The first trial was a dose escalation single dose placebo controlled trial in which doses ranging from 0.1 to 60 mg were evaluated. For each dose, 4 male volunteers were treated with active medication and 2 with placebo in a parallel design except for the 60 mg dose, which was evaluated in a crossover trial. Estradiol results from placebo treated volunteers were pooled together and showed the expected 24 h circadian rhythm. For ARIMIDEX treated patients, results showed a dose-dependent suppression of estradiol with doses of 7.5 mg and higher producing suppression of 80% or greater from baseline. For all doses, maximum suppression occurred between 6 and 12 h after dosing and was sustained for at least 24 h. Evaluation of the 60 mg dose included a 48 h follow-up period, and again, the estradiol level was sustained for this period.

In the second trial, healthy postmenopausal female volunteers were randomized to receive either 0.5 or 1 mg of ARIMIDEX for 14 consecutive days. Mean estradiol levels corresponding to trial designated time points are shown in Fig. 1. Both doses were able to maximally suppress estradiol to levels close to the limit of detection of the assay by day 3 or 4 of treatment. This degree of suppression was maintained for the duration of treatment and for at least 6 days after therapy was stopped. Although 1 mg of ARIMIDEX suppressed estradiol to a greater degree, this difference was not statistically different.

The 3 mg ARIMIDEX dose was evaluated in a double blind placebo controlled crossover trial in which healthy, postmenopausal women each took a single dose to allow for pharmacokinetic and endocrine assessments to be made over the ensuing 3 days. Then, 3 mg was given daily for the next 7 days. Estradiol suppression achieved with 3 mg per day of ARIMIDEX and placebo is shown in Fig. 2. A single dose of 3 mg quickly suppressed estradiol levels which was maintained for the duration of the dosing period. In this trial, estradiol began to rise 2 days after discontinuing the last dose. Unlike estradiol, the circulating estrone levels were only minimally suppressed relative to placebo with a single 3 mg dose of ARIMIDEX,

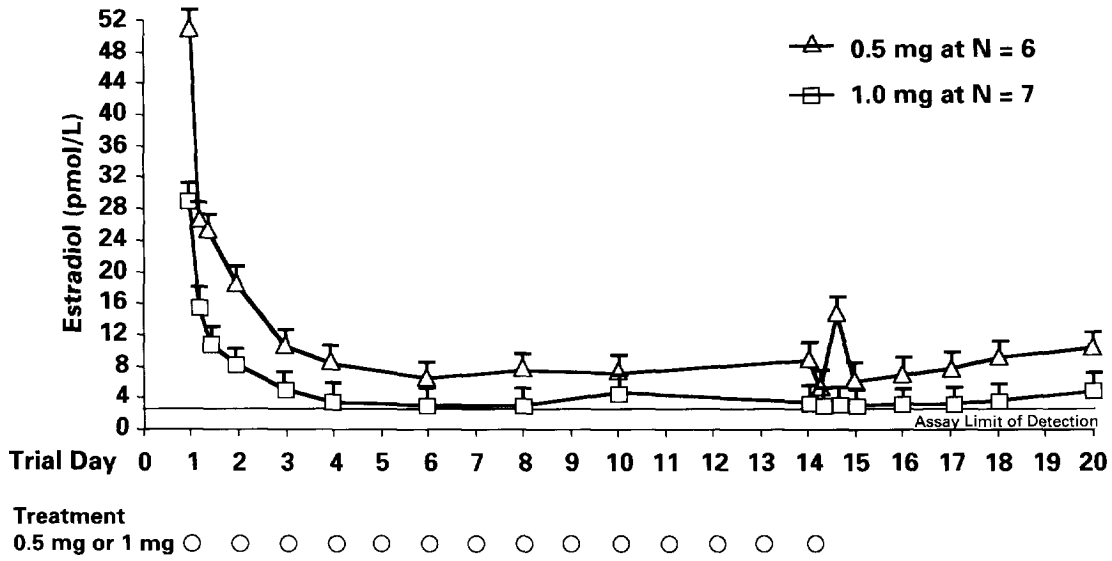

Fig. 1. Mean estradiol levels (±SD) with daily administration of 0.5 and 1 mg of ARIMIDEX.

although further suppression was seen after daily dosing. This suggests that a longer dosing period is required to maximally suppress estrone or alternately may reflect the poorer sensitivity of the estrone assay. Androstenedione showed no change in circulating levels compared with the results from the placebo treated patients.

In the fourth trial, postmenopausal women with advance breast cancer first took 5 mg of ARIMIDEX daily for 14 days. If they tolerated the medication and if their ACTH results were normal, then they took 10 mg for 14 more days. Upon completion of this study, patients were allowed to continue treatment with 10 mg daily until disease progression. (Mean estradiol levels are shown in Fig. 3).

The 5 mg dose lowered estradiol to the limit of detection of the assay, and as expected, this degree of suppression was maintained with 10 mg throughout the dosing period through 171 days. Estrone was significantly suppressed to 69–86% of baseline and estrone sulfate to 83–92% of baseline when measured after 14 days of dosing with 5 mg of ARIMIDEX and after 14 days of dosing with 10 mg of ARIMIDEX, respectively. For androstenedione, no changes in circulating levels were seen with continuous dosing with either 5 or 10 mg of ARIMIDEX.

For each of the doses evaluated in the multiple dose trials, the percent estradiol suppression from baseline at steady state showed suppression to greater than 80% of baseline. Using this method for assessing a dose–response, we were unable to distinguish between the ARIMIDEX doses of 0.5–10 mg. For this reason,

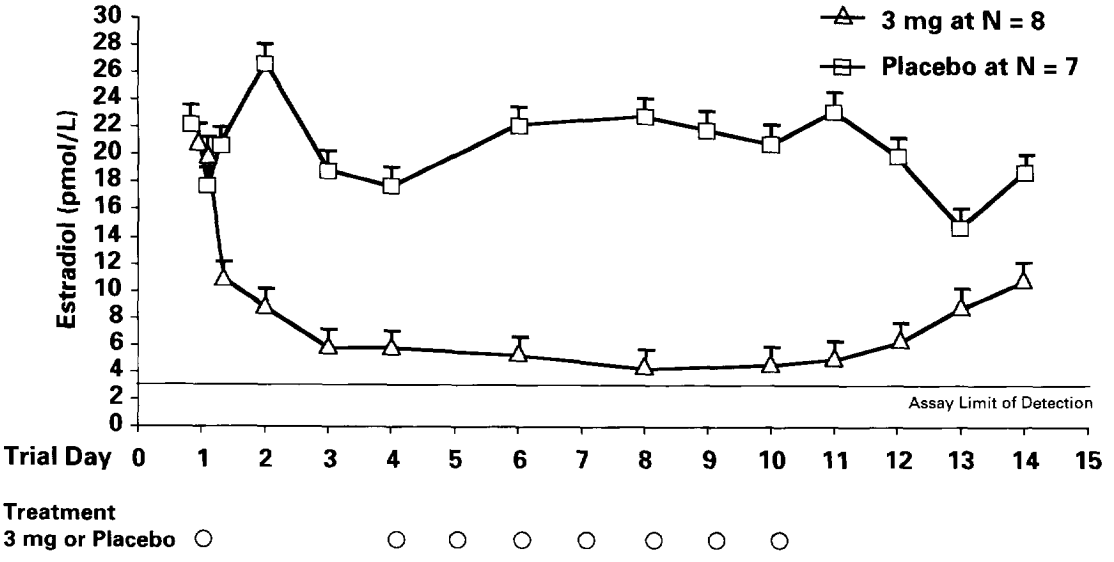

Fig. 2. Mean estradiol levels (±SD) with daily administration of 3 mg of ARIMIDEX or placebo.

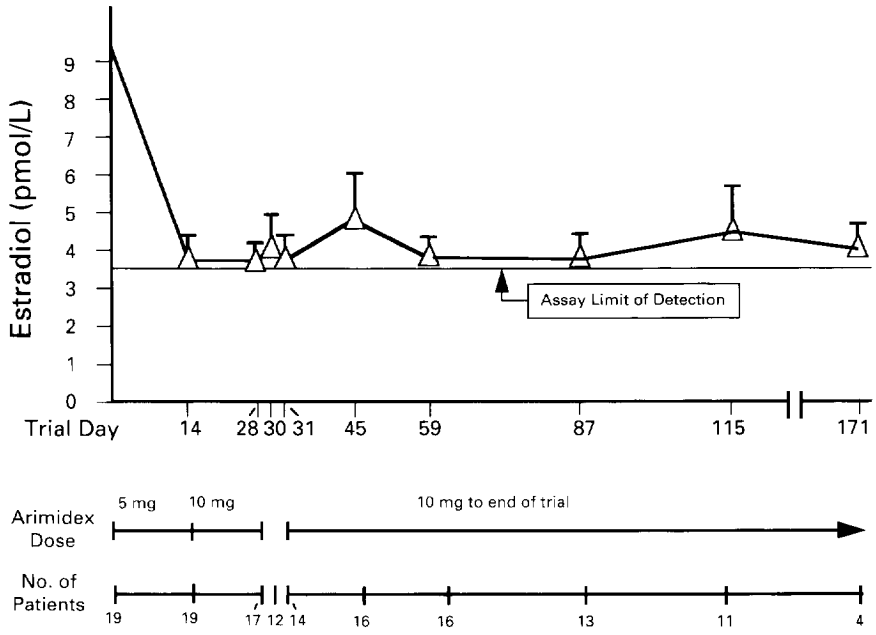

Fig. 3. Mean estradiol levels (± SD) with daily administration of ARIMIDEX 5 mg followed by ARIMIDEX 10 mg.

the absolute estradiol suppression at steady state was examined to determine the number of subjects who suppressed estradiol to the limit of detection of the assay.

With the 0.5 mg dose, only 2 of the 6 volunteers achieved suppression close to the limit of detection of the assay. In comparison, with the 1 mg dose all patients (7 of 7) achieved estradiol suppression to the assay limit of detection. The majority of patients (6 of 8) in the 3 mg trial achieved suppression to the limit of detection of the assay. For the 5 mg dose, 18 of 19 patients and for the 10 mg dose 17 of 17 patients suppressed estradiol to the limit of detection of the assay. This would indicate that 1 mg is the minimal dose needed to suppress estradiol to the limit of detection of a sensitive estradiol assay. Given the limitation of the assays, we cannot determine if doses higher than 1 mg suppress estradiol to an even greater degree. If the degree of estradiol suppression is important to achieve clinical benefit to breast cancer patients, the benefit of doses higher than 1 mg would need to be assessed through a clinical trial.

ARIMIDEX SELECTIVITY

The cortisol and aldosterone response to ACTH stimulation testing at baseline and after 14 days on 5 and 10 mg of ARIMIDEX was evaluated. Patients who completed this study continued in the extension study and had ACTH stimulation testing after 4 and 12 weeks more of treatment. At all time points evaluated, the cortisol and aldosterone levels prior to ACTH stimulation were similar, and the rise in cortisol at 30 and 60 min after the injection of ACTH was similar to the pre-treatment values for the 5 and 10 mg doses and at different treatment times with 10 mg of ARIMIDEX.

ARIMIDEX PHARMACOKINETICS

ARIMIDEX was well absorbed following oral administration by oral tablet or solution, with maximum plasma ZD1033 concentrations occurring within 2 h of dosing. Plasma concentrations of ARIMIDEX increased proportionately with increasing doses of the drug. ARIMIDEX was cleared slowly with an estimated half-life of 50 h. The drug was highly metabolized and less than 10% of the dose was cleared in urine as unchanged drug. In general, pharmacokinetic parameters of ARIMIDEX display exceptionally low inter- and intra-subject variability.

After ARIMIDEX administration of daily doses ranging from 0.5 to 10 mg daily in healthy volunteers or patients, 90–95% of plasma steady-state concentrations were attained by the 10th ARIMIDEX dose. With daily dosing of ARIMIDEX, steady-state accumulation in plasma was approx. 3–4-fold. There was no evidence of time- or dose-dependency in ARIMIDEX pharmacokinetic parameters, and multiple-dose plasma concentrations of ARIMIDEX can be predicted by using linear pharmacokinetic models and single-dose data.

RESULTS IN PATIENTS WITH ADVANCED BREAST CANCER

Nineteen patients with breast cancer entered the fourth trial, which evaluated 5 and 10 mg of ARIMIDEX. Those who completed the trial were eligible to

enter the extension study at the discretion of the investigator. Possible participation in the extension study was offered as an inducement to patients to enter the first study. All 19 women were postmenopausal with a mean age of 58.1 years (range 44–81). Eighty-four were either estrogen-receptor (ER) or progesterone-receptor (PR) positive, and 11% were ER and PR negative;, receptor status in the remainder was unknown. Sites of metastasis at entry were bone (58%); nodal (37%); skin (32%); and viscera (53%). All have received prior treatment for advanced breast cancer with an average of 2.6 previous systemic treatments.

Overall, two patients were withdrawn from the study during the 10 mg treatment period because of breast cancer progression. Seventeen patients were therefore eligible to enter the extension study and all elected to be enrolled. To date, there have been 14 relapses: 8 (47%) relapsed after 3 months or less of treatment, 2 (12%) after 4–6 months of treatment, 2 (12%) after 7–12 months of treatment, 1 (6%) after 13–18 months of treatment, and 1 (6%) after 19–24 months of treatment. Three patients (18%) continued treatment after 20, 21, and 23 months of treatment, respectively. Although this trial was not an efficacy study, and response information was not obtained, the length of time these patients have been able to remain on treatment is encouraging given the number of prior treatments they received and the extent of their disease.

SAFETY

All doses evaluated up to 10 mg were well tolerated and, there were no serious adverse events attributable to ARIMIDEX. No clinical or laboratory evidence of adrenal insufficiency was observed. Additional data in large clinical trials are needed to confirm the safety of ARIMIDEX.

CONCLUSION

ARIMIDEX is a potent aromatase inhibitor with dose of 1 mg and higher capable of suppressing estradiol to the limit of detection of a sensitive estradiol assay. The drug is selective and well tolerated. Phase III studies are underway to evaluate the efficacy of ARIMIDEX in the treatment of postmenopausal women with breast cancer. Although the efficacy and safety of ARIMIDEX needs to be demonstrated in large clinical trials, the results thus far show this drug to be an exciting and promising treatment for women with advanced breast cancer.

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