Clinical and Biochemical Consequences of CYP17A1 Inhibition with Abiraterone Given with and without Exogenous Glucocorticoids in Castrate Men with Advanced Prostate Cancer

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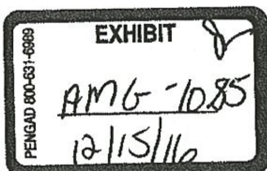
Context: Abiraterone acetate is a small-molecule cytochrome P450 17A1 (CYP17A1) inhibitor that is active in castration-resistant prostate cancer.

Objective: Our objective was to determine the impact of abiraterone with and without dexamethasone treatment on *in vivo* steroidogenesis.

Design and Methods: We treated 42 castrate, castration-resistant prostate cancer patients with continuous, daily abiraterone acetate and prospectively collected blood and urine before and during abiraterone treatment and after addition of dexamethasone 0.5 mg daily.

Results: Treatment with single-agent abiraterone acetate was associated with accumulation of steroids with mineralocorticoid properties upstream of CYP17A1. This resulted in side effects, including hypertension, hypokalemia, and fluid overload, in 38 of 42 patients that were generally treated effectively with eplerenone. Importantly, serum and urinary androgens were suppressed by more than 90% from baseline. Urinary metabolites of 17-hydroxypregnenolone and 17-hydroxyprogesterone downstream of 17α-hydroxylase remained unchanged. However, 3α5α-17-hydroxypregnanolone, which can be converted via the backdoor pathway toward 5α-dihydrotestosterone, increased significantly and correlated with levels of the major 5α-dihydrotestosterone metabolite androsterone. In contrast, urinary metabolites of 11-deoxycortisol and active glucocorticoids declined significantly. Addition of dexamethasone to abiraterone acetate significantly suppressed ACTH and endogenous steroids, including 3α5α-17-hydroxypregnanolone.

Conclusion: CYP17A1 inhibition with abiraterone acetate is characterized by significant suppression of androgen and cortisol synthesis. The latter is associated with a rise in ACTH that causes raised mineralocorticoids, leading to side effects and incomplete 17α-hydroxylase inhibition. Concomitant inhibition of 17,20-lyase results in diversion of 17-hydroxyprogesterone metabolites toward androgen synthesis via the backdoor pathway. Addition of dexamethasone reverses toxicity and could further suppress androgens by preventing a rise in substrates of backdoor androgen synthesis. **(*J Clin Endocrinol Metab* 97: 507–516, 2012)**



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Abbreviations: An, Androsterone; AR, androgen receptor; CRPC, castration-resistant prostate cancer; CYP17A1, cytochrome P450 17A1; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; DOC, 11-deoxycorticosterone; 3α5α-17HP, 3α5α-17OH-pregnanolone; LC-MS/MS, liquid chromatography/tandem mass spectrometry; 17OHP, 17-hydroxyprogesterone; PSA, prostate-specific antigen; THALDO, 3α,5β-tetrahydroaldosterone; THS, tetrahydro-11-deoxycortisol.

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Prostate cancer is the second most common cause of male cancer-related death in the Western world (1). Treatment-naive prostate cancer is usually a hormone-driven disease, with a response to castration observed in more than 90% of patients. The median duration of response is 18 months. Overwhelming evidence now confirms that in a significant proportion of patients, relapse with castration-resistant prostate cancer (CRPC) occurs secondary to reactivation of androgen receptor (AR) signaling, including by serum androgens from nongonadal sources (2). Cytochrome P450 17A1 (CYP17A1) is a key enzyme in cortisol synthesis via its 17α-hydroxylase activity and plays a central role in androgen biosynthesis with its 17,20-lyase activity catalyzing the conversion of 17-hydroxypregnenolone to the main androgen precursor dehydroepiandrosterone (DHEA) (3, 4). CYP17A1 is expressed in the gonads but also at extragonadal sites including the prostate (5–7) where it might contribute to intracrine hormone synthesis.

Abiraterone is a rationally designed, small-molecule inhibitor of CYP17A1 (8, 9). The specificity of abiraterone for inhibition of 17,20-lyase *vs.* 17α-hydroxylase is low (1.4-fold, IC_{50} = 2.9 nM compared with 4 nM) (10), and treatment with abiraterone acetate would therefore be expected to cause a rise in ACTH with a consequent increase in 11-deoxycorticosterone (DOC) and corticosterone, mimicking the effects observed in patients with congenital adrenal hyperplasia due to inactivating *CYP17A1* mutations (3). To date, it has proven difficult to develop a small-molecule therapeutic that specifically inhibits only the 17,20-lyase activity of CYP17A1 (11).

When administered to noncastrate men, abiraterone acetate resulted in suppression of testosterone with a subsequent LH surge that overcame inhibition of gonadal testosterone synthesis (12). We subsequently reported that continuous inhibition of CYP17A1 with oral abiraterone acetate in chemotherapy-naive, CRPC patients was safe and significantly suppressed serum androgens and estrogens (6, 13). Importantly, we and others reported significant antitumor activity in phase I/II trials with single-agent abiraterone acetate after multiple previous lines of hormone therapy, including ketoconazole, and in chemotherapy-treated patients (13–15). Recently, abiraterone acetate was given regulatory approval for the treatment of men with advanced prostate cancer progressing after docetaxel after a phase III study showed that combined treatment with abiraterone acetate and prednisone conferred a survival benefit when compared with prednisone alone (16).

We and others previously used RIA to measure serum androgens. Androstenedione and DHEA sulfate (DHEAS) were suppressed to below the lower limits of detection (2 ng/dl and 15 μg/dl, respectively), and DHEA declined 3-fold; however, because cross-reactivity with abiraterone was observed in this assay, the detection of DHEA in patients on abiraterone acetate could be artifactual (6, 15). A liquid chromatography/tandem mass spectrometry (LC-MS/MS) assay was used to measure serum testosterone levels that declined to below the lower limit of sensitivity (1 ng/dl) in all patients (6, 15). However, these studies have incompletely dissected the biochemical consequences of treatment with abiraterone acetate. We here report the first detailed, mass spectrometry-based analysis of the steroidogenic effects of CYP17A1 inhibition in samples taken from medically castrated patients treated with single-agent abiraterone acetate and with the combination of abiraterone acetate and dexamethasone.

Patients and Methods

Patients

All the patients included in this prospectively planned analysis were enrolled into the continuous daily study of abiraterone acetate performed at the Royal Marsden Hospital (RMH), London, UK (COU-001, www.clinicaltrials.gov identifier NCT00473512). All patients were castrate (serum testosterone < 50 ng/dl) for the duration of the study (ongoing treatment with a LHRH analog), had an Eastern Co-operative Oncology Group (ECOG) performance status of 0 or 1, had not received previous treatment with chemotherapy or radionuclides, and had progressive disease as defined by prostate-specific antigen (PSA) Working Group I (17). The ethics review committees of the RMH approved this study, and all patients gave informed consent. The antitumor activity and safety data observed in this study were reported previously (6, 13).

Treatment and procedures

Abiraterone acetate powder was administered in four 250-mg capsules to fasted patients daily in 28-d cycles. Safety evaluations were conducted at baseline, weekly for the first two cycles and every cycle thereafter and included a physical examination and complete blood count, clotting, serum creatinine, electrolytes, and liver function tests. All adverse events were graded according to the U.S. National Cancer Institute common toxicity criteria version 3.0. Toxicity related to elevated mineralocorticoid levels was managed with the selective mineralocorticoid receptor antagonist eplerenone (50–200 mg/d), and treatment with glucocorticoids to suppress ACTH was only used if mineralocorticoid antagonism did not reverse these toxicities. Spironolactone was not used because it is an agonist for wild-type AR (18). Abiraterone acetate was continued until PSA progression as defined by PSA Working Group I (17). Patients were then given the option to continue abiraterone acetate in combination with dexamethasone 0.5 mg daily, which as the standard glucocorticoid preparation for treating CRPC at our institution (19) was used in preference to other steroids to allow the evaluation of antitumor activity. Eplerenone was discontinued after initiation of dexamethasone when toxicities related to mineralocorticoid excess resolved. Patients continued treatment on abiraterone acetate and dexamethasone until PSA, radiological (20), or clinical progression; withdrawal of consent; or death (6, 13).

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Patients were given the option to consent to additional blood draws for the evaluation of serum androgens and plasma ACTH weekly for the first two cycles, on d 1 every cycle thereafter until progression on single-agent abiraterone acetate and after addition of dexamethasone to abiraterone acetate, weekly for the first cycle and monthly thereafter. Patients were also given the option to consent to and provide a 24-h urine sample for steroid metabolite analyses before treatment, after a minimum of 28 d continuous dosing (d 1, cycle 2 or 3) and on d 1, cycle 6 or 7 (Supplemental Fig. 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

Measurement of ACTH and steroids

Plasma ACTH was measured by the RMH Academic Biochemistry Laboratories with a solid-phase two-site sequential chemiluminescent immunometric assay (LKAC1) using an IMMULITE 1000 autoanalyzer (Siemens Heathcare Diagnostics Products Ltd., Surrey, UK). The analytical sensitivity was 9 pg/ml. The intraassay precision and interassay precision was 6.1 and 9.4%, respectively, at 51 pg/ml. Serum testosterone, DHEAS, and androstenedione were measured using a modified LC-MS/MS assay developed by Esoterix (Calabasas Hills, CA) with lower limits of sensitivity of 0.05 ng/dl for testosterone, 0.1 ng/dl for DHEAS, and 0.1 ng/dl for androstenedione.

Twenty-seven urinary steroids were measured by gas chromatography/mass spectrometry in selected-ion-monitoring mode after solid-phase extraction and derivatization as described previously (21, 22). For simplification, the 17-deoxy-21-carbon steroids that represent metabolites of DOC, corticosterone, and 18-hydroxycorticosterone are described as mineralocorticoid precursor metabolites. Similarly, the 17-hydroxy-21-carbon steroids derived from active glucocorticoids are summarized as glucocorticoid metabolites. The sum of the urinary glucocorticoid metabolites α-cortol, β-cortol, α-cortolone, and β-cortolone is reported as cortols plus cortolones. The 19-carbon steroids represent the sum of androgen and androgen precursor metabolites (Table 1).

Statistics

The median time on treatment, defined as the time from start until discontinuation of abiraterone acetate treatment or addition of dexamethasone, for the intention-to-treat population with censoring of patients who did not have progressive disease was calculated using the Kaplan-Meier method. The significance of the difference between pretreatment *vs.* on-treatment urinary steroid levels and levels on-treatment *vs.* after addition of dexamethasone was determined using the sign test (calculated using Stata version 10.1). This nonparametric method tested the null hypothesis that the median of the differences of paired data is 0. Correlations of nonparametric data are defined by the Spearman correlation coefficient (r) calculated using Prism statistical software (version 5; GraphPad, San Diego, CA). An r of 1 is a perfect correlation. All P values are two sided, and a result was considered significant when the P value was <0.05.

Results

Single-agent abiraterone acetate is associated with a syndrome of secondary mineralocorticoid excess

Forty-two patients were treated for a total of 10,359 d (1479 wk) with single-agent 1000-mg abiraterone acetate. This cohort was presented previously when five patients continued on treatment (13), but now none of these patients remain on single-agent abiraterone acetate. Abiraterone acetate was discontinued prematurely because of rapid disease progression in four patients and for other reasons in five patients (two for deranged liver function tests, one due to acute-onset idiopathic polyneuropathy, another due to worsening asthma and eosinophilia, and the fifth for a diagnosis of colorectal carcinoma requiring chemotherapy). Three patients required addition of dexamethasone to abiraterone acetate due to side effects of secondary mineralocorticoid excess. The remaining 30 patients continued treatment on abiraterone acetate until a confirmed rise in PSA, at which time dexamethasone was added to evaluate reinduction of sensitivity as reported previously (Supplemental Fig. 1) (6, 13). The median time on treatment calculated using the Kaplan-Meier method was 231 d (95% confidence interval = 122–307).

We here present in detail the clinical manifestations and management of side effects attributable to mineralocorticoid excess secondary to CYP17A1 inhibition in patients receiving abiraterone acetate without exogenous glucocorticoids. Four of 42 patients received abiraterone acetate with no clinical evidence of mineralocorticoid excess (and no rise in PSA) for 38, 65, 253, and 392 d. Dexamethasone was added before an attempt with eplerenone due to intractable migrainous headaches in two patients: in one on d 72 in the presence of grade 3 hypokalemia (2.8 mmol/liter), grade 2 hypertension, and grade 1 lower limb edema and in the other on d 58 in the presence of grade 1 hypokalemia. The other 36 patients developed clinical evidence of a syndrome of mineralocorticoid excess and were treated with eplerenone that was initiated after a median of 28 d (range, 6–387) (Fig. 1A). Thirty-five patients had hypokalemia at initiation of eplerenone (Fig. 1B), whereas one had normal serum potassium, grade 1 hypertension, and grade 1 lower limb edema (Fig. 1C). In addition to hypokalemia, 10 patients had a raised blood pressure, five patients had a raised blood pressure and grade 1 lower limb edema, and five patients had grade 2 lower limb edema. One patient had grade 3 lower limb edema, grade 3 pulmonary edema, and a serum potassium of 3.4 mmol/liter (Fig. 1C) that did not resolve with eplerenone and required addition of dexamethasone 0.5 mg daily to control his symptoms. Eplerenone up to a maximum daily dose of 200 mg (Fig. 1D) resolved the clinical syndrome of mineralocorticoid excess in the other 35 patients.

Continuous daily abiraterone acetate leads to ACTH-driven mineralocorticoid excess

We and others have previously used RIA to identify a significant increase in serum DOC, corticosterone, and

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TABLE 1. Percent change in urinary steroid metabolite excretion with continuous daily abiraterone acetate and after addition of dexamethasone 0.5 mg once daily

	Baseline *vs.* single-agent abiraterone acetate (n = 21)			Abiraterone acetate *vs.* after addition of dexamethasone (n = 7)		
	% change from baseline			% change from single agent abiraterone		
	Range	Median	*P* value	Range	Median	*P* value
Urinary 17-deoxy-21-carbon steroids						
Pregnenolone metabolites						
Pregnenediol (5-PD)	249 to 4400	842	<0.0001	−99 to −77	−93	0.0156
Progesterone metabolites						
Pregnanediol (PD)	381 to 6106	1919	<0.0001	−100 to −62	−91	0.0156
Mineralocorticoid precursor metabolites						
Tetrahydro-DOC (TH-DOC)	342 to 8769	3069	<0.0001	−99 to −67	−93	0.0156
5α-Tetrahydro-DOC (5α-TH-DOC)	−63 to 3535	882	<0.0001	−100 to −61	−92	0.0156
Tetrahydrocorticosterone (THB)	662 to 8091	2997	<0.0001	−100 to −62	−95	0.0156
Tetrahydro-11-dehydrocorticosterone (THA)	1159 to 9658	4488	<0.0001	−100 to −62	−94	0.0156
5α-Tetra-11-dehydrocorticosterone (5α-THA)	349 to 4581	1819	<0.0001	−99 to −64	−96	0.0156
5α-Tetrahydrocorticosterone (5α-THB)	659 to 14222	3317	<0.0001	−100 to −84	−99	0.0156
Mineralocorticoid metabolites						
3α5β-tetrahydro-aldosterone (THALDO)	−100 to 49	−40	0.0118	−92 to 267	−21	>0.9999
Urinary 17-hydroxy-21-carbon steroids						
17-Hydroxypregnenolone metabolites						
5-Pregnenetriol (5-PT)	−87 to 330	−15	0.1892	−99 to −68	−95	0.0156
17-hydroxyprogesterone (17OHP) metabolites						
Pregnanetriol (PT)	−85 to 215	−36	0.3833	−98 to −53	−82	0.0156
17-OH-Pregnanolone (17HP)	−75 to 314	9	>0.9999	−99 to 0	−81	0.0313
3α5α-17-OH-pregnanolone (3α5α-17HP)	−60 to 589	100	0.0002	−100 to −50	−99	0.0156
Pregnanetriolone	−75 to 800	29	0.1892	−100 to −33	−80	0.0156
11-Deoxycortisol metabolites						
Tetrahydro-11-deoxycortisol (THS)	−93 to 71	−73	<0.0001	−100 to −59	−90	0.0156
Glucocorticoid metabolites						
Tetrahydrocortisol (THF)	−97 to 2	−86	<0.0001	−99 to −84	−94	0.0156
5α-Tetrahydrocortisol (5α-THF)	−96 to 27	−85	<0.0001	−100 to −87	−97	0.0156
Cortisol	−100 to 138	−44	0.0015	−100 to −100	−100	0.0313
Cortols and cortolones	−89 to −30	−68	<0.0001	−100 to −80	−94	0.0156
Tetrahydrocortisone (THE)	−96 to 16	−80	<0.0001	−99 to −83	−95	0.0156
Urinary 19-carbon steroids						
Metabolites of androgens and androgen precursors						
DHEA	−99 to −35	−97	<0.0001	−100 to 633	−43	>0.9999
Androsterone (An)	−98 to −39	−94	<0.0001	−94 to 100	−39	>0.9999
Etiocholanolone (ETIO)	−100 to 179	−65	00.0118	−75 to 90	25	0.6875

A significance in the difference between metabolites is denoted by a *P* value < 0.05 calculated using the sign test.

11-deoxycortisol levels after treatment with abiraterone acetate (6, 15). This increase was associated with a significant rise in ACTH (median, 660% increase; range, 283-1416% increase; *P* value < 0.0001, sign test) from a median of 17 pg/ml (range, <9–50 pg/ml) before treatment to 124 pg/ml (range, 46–370 pg/ml) on treatment (n = 26). To further study the effect of abiraterone acetate, we have used gas chromatography/mass spectrometry to comprehensively study urinary steroid metabolites in 24-h urine collections before treatment and after one or two cycles (28–56 d) of single-agent abiraterone acetate. Twenty-one patients consented to these analyses and provided 24-h urine samples. All urinary mineralocorticoid precursor metabolites (upstream of CYP17A1) increased markedly on treatment; however, the metabolite of aldosterone, 3α,5β-tetrahydroaldosterone (THALDO) declined (Fig. 2A). The median of the sum of urinary mineralocorticoid metabolites excluding THALDO rose 26-fold after one or two cycles of treatment from 847 μg/24 h (range, 388-1503 μg/24 h) to 22,752 μg/24 h (range, 7729–75535 μg/24 h). Changes in individual metabolites and their significance calculated using the sign test are reported in Table 1. In contrast, and explaining the rise in ACTH, all metabolites of active glucocorticoids declined significantly (Table 1) with a 5-fold decrease in the median of the sum of metabolites from 9086 μg/24 h (range,

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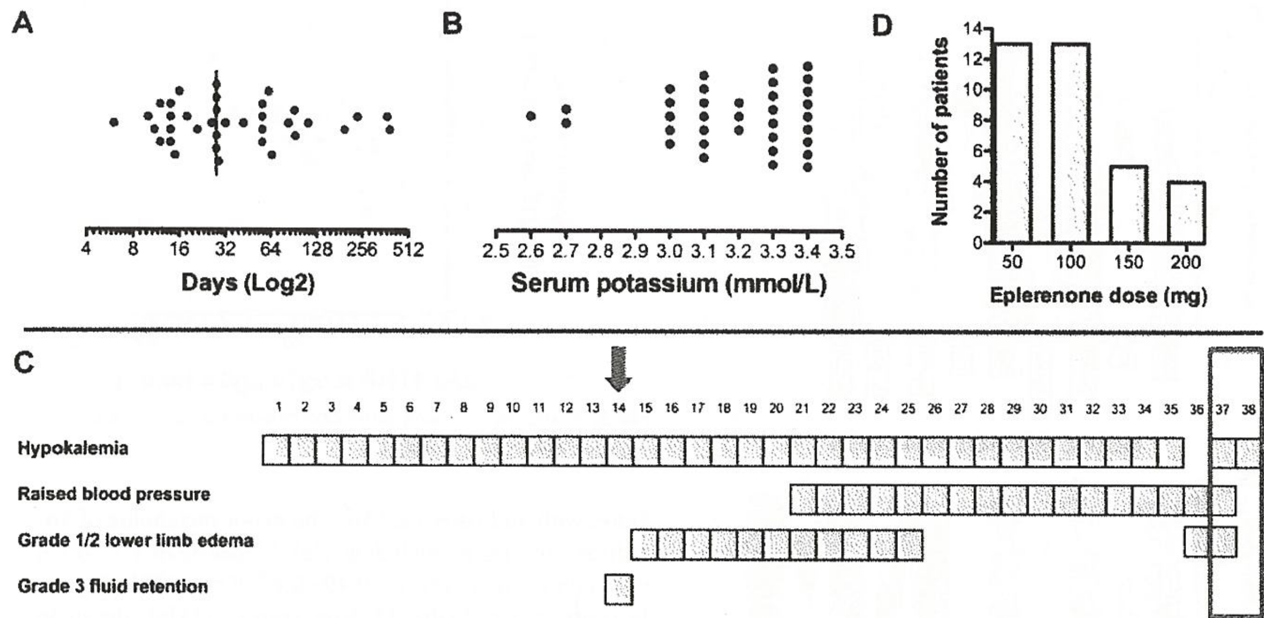

FIG. 1. Syndrome of mineralocorticoid excess in patients (n = 38) treated with single-agent abiraterone acetate. A, Scatter plot showing number of patients and days after starting single-agent abiraterone acetate that eplerenone was commenced (n = 36; *vertical red line* marks median value of 28 d) (log2 scale); B, scatter plot showing number of patients and serum potassium level at initiation of eplerenone (n = 36); C, clinical manifestation of mineralocorticoid excess at start of eplerenone (n = 36) or dexamethasone (n = 2). Each column represents a patient, and *shaded boxes* signify presence of toxicity. Patient numbers are random. Patients 37 and 38 (*red box*) represent the two patients administered dexamethasone before a trial of eplerenone, and patient 14 (*red arrow*) represents the one patient who required dexamethasone despite a trial with eplerenone. D, Number of patients and dose of eplerenone that resolved the clinical syndrome of mineralocorticoid excess (n = 35).

4645–17633 μg/24 h) before treatment to 2154 μg/24 h (range, 426-7416 μg/24 h) after one or two cycles of abiraterone treatment (Fig. 2B). A one-way ANOVA showed no evidence of a difference in mean urinary excretion of mineralocorticoid precursor metabolites and the dose of eplerenone required to control toxicity [$F_{(5,15)} = 0.27$; $P = 0.9214$]. We also evaluated urinary steroid metabolites from nine patients who continued single-agent abiraterone acetate for at least five or six cycles (140–168 d) and did not observe a significant difference in urinary metabolites compared with after one or two cycles (Fig. 2).

Abiraterone significantly suppresses urinary androgen metabolites and serum androgens

The median of the sum of urinary 19-carbon steroids, *i.e.* androgen metabolites, in castrate men before starting abiraterone acetate was 735 μg/24 h (range, 127-6755 μg/24 h). After 28–56 d treatment with single-agent abiraterone acetate, urinary androgen metabolites were all significantly suppressed (Fig. 2C and Table 1) with a 20-fold decrease to 37 μg/24 h (range, 6–896 μg/24 h). There was no significant further change from after one or two cycles to after five or six cycles of single-agent abiraterone acetate (n = 9) (Fig. 2C).

We then measured circulating androgen levels using an ultrasensitive LC-MS/MS assay (Esoterix) in samples collected before and on treatment and at progression. Ninety-three on-treatment samples from 32 patients were available for analysis. Serum testosterone declined to a median of 0.26 ng/dl with a range of <0.05–0.90 ng/dl (decline to <0.05 ng/dl in five of 32 patients). Serum DHEAS declined to a median of 0.2 ng/dl with a range of <0.1–9.4 ng/dl (<0.1 ng/dl in 14 of 32 patients). Serum androstenedione declined to a median of 0.32 ng/dl with a range of <0.1–1.58 ng/dl (<0.1 ng/dl in three of 19 patients). Importantly, there was no rise in serum testosterone or DHEAS in the 11 patients evaluated at disease progression on abiraterone acetate using these ultrasensitive assays, in contrast to previously reported changes at progression on ketoconazole (23).

CYP17A1 inhibition with abiraterone is associated with increased substrates of the backdoor pathway of DHT synthesis

Urinary metabolites of 17-hydroxypregnenolone and 17-hydroxyprogesterone (17OHP) did not change significantly with abiraterone acetate, but there was a significant increase in the 17OHP metabolite 3α5α-17OH-pregnanolone (3α5α-17HP) from a median of 4 μg/24 h (range, 1–13.6 μg/24 h) to 8 μg/24 h (range, 1.7–36.1 μg/24 h) on abiraterone acetate (median intra-patient change = 100%, P value for significance of rise = 0.0002, sign test) (Table 1 and Fig. 2B). Interestingly, 3α5α-17HP levels on abiraterone acetate showed a significant corre-

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