REVIEW

Antiandrogen withdrawal syndrome (AAWS) in the treatment of patients with prostate cancer

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Abstract

Antiandrogen withdrawal syndrome is an unpredictable event diagnosed in patients with hormone-sensitive prostate cancer treated with combined androgen blockade therapy. It is defined by prostate-specific antigen value reduction, occasionally associated with a radiological response, that occurs 4–6 weeks after first-generation antiandrogen therapy discontinuation. New-generation hormonal therapies, such as enzalutamide and abiraterone acetate, improved the overall survival in patients with metastatic castration-resistant prostate cancer, and recent trials have also shown the efficacy of abiraterone in hormone-sensitive disease. In the last few years, several case reports and retrospective studies suggested that the withdrawal syndrome may also occur with these new drugs. This review summarizes literature data and hypothesis about the biological rationale underlying the syndrome and its potential clinical relevance, focusing mainly on new-generation hormonal therapies. Several *in vitro* studies suggest that androgen receptor gain-of-function mutations are involved in this syndrome, shifting the antiandrogen activity from antagonist to agonist. Several different drug-specific point mutations have been reported. The association of the withdrawal syndrome for enzalutamide and abiraterone needs confirmation by additional investigations. However, new-generation hormonal therapies being increasingly used in all stages of disease, more patients may experience the syndrome when stopping the treatment at the time of disease progression, although the clinical relevance of this phenomenon in the management of metastatic castration-resistant prostate cancer remains to be defined.

Key Words

- ▶ antiandrogen withdrawal syndrome
- ▶ prostate cancer
- ▶ bicalutamide
- ▶ enzalutamide
- ▶ abiraterone

Endocrine-Related Cancer
(2018) 25, R1–R9

Introduction

In recent years, the treatment of patients with metastatic prostate cancer (PCa) has radically changed, with the availability of new antiandrogen hormonal therapies. However, this disease still remains a major health issue in the Western countries, being the second leading cause of cancer-related death in men (Siegel *et al.* 2016). The natural

history of metastatic PCa consists usually of two phases. In the first phase, usually denominated 'hormone-sensitive disease', the disease is usually effectively controlled by androgen deprivation therapy (ADT). The crucial role of androgen receptor (AR) in disease development and progression (Parker *et al.* 2015) makes PCa extremely

sensitive to surgical or biochemical castration. Moreover, recent findings showed that in patients with high-risk and/or high-volume hormone-sensitive metastatic disease, the addition of docetaxel to ADT when compared to ADT alone induces a significant improvement in the overall survival (Sweeney *et al.* 2015, James *et al.* 2016). Similar results have been recently presented for the combination of abiraterone acetate and ADT (Fizazi *et al.* 2017, James *et al.* 2017). Despite the initial therapeutic success, after a median of 24–36 months (Scher *et al.* 2004), resistance to ADT eventually arises, that delimits the beginning of the second phase, the ‘castration-resistant prostate cancer’ (CRPC). It was previously believed that the development of CRPC was invariably associated with complete resistance to antiandrogen therapies, because it was believed that PCa cell growth was independent from AR activation. Currently, there is evidence supporting a key role of the AR in all the phases of PCa, and AR and intra-tumoral steroidogenesis modifications drive the evolution to CRPC. Neoplastic cells acquire the capability to grow in an environment characterized by low androgens levels, because of the upregulation of specific enzymes involved in androgen synthesis, such as CYP17 α -hydroxylase and C17–20-lyase (CYP17), AR gene overexpression and mutations, AR splice variants expression and increased expression of transcriptional coactivators (Buttiglierio *et al.* 2015, McCrea *et al.* 2016).

These findings suggest that the transition from hormone-sensitive disease to CRPC is not related to a real androgen resistance, but rather to functional adaptation of PCa cells. Consequently, there is a continuous response to hormonal stimulation, despite the persisting, dramatic reduction of circulating androgen levels (Buttiglierio *et al.* 2015). The better understanding of tumor biology and progression led to the development of new-generation hormonal therapies (such as abiraterone and enzalutamide), able to interfere with AR signaling pathway or to suppress CYP17 activity.

The antiandrogen withdrawal syndrome (AAWS) is defined as a further significant (>50%) reduction in prostate-specific antigen (PSA) values after the discontinuation of antiandrogen therapy, in the context of combined androgen blockade (CAB) treatment. CAB, also called combined hormone blockade or total hormone blockade, is the combination of an antiandrogen and surgical or biochemical castration. Initially observed in patients withholding the antiandrogen flutamide (Kelly & Scher 1993), AAWS has been subsequently documented in patients treated with other first-generation antiandrogen drugs, such as bicalutamide and nilutamide.

From a biological point of view, AAWS is strictly associated with specific AR mutations that are inducing a gain of function of AR and the subsequent conversion of antiandrogens into full-fledged androgens, aberrantly replacing testosterone and DHT.

Before the advent of new-generation hormonal therapies, in patients withholding bicalutamide and continuing ADT in the presence of serological progression only, AAWS was used to justify the delay of the beginning of chemotherapy with docetaxel.

The observed response rate can be as high as 30% and might be directly associated with treatment duration with AR blockers (Paul & Breul 2000). With the new-generation hormonal therapies, such as enzalutamide and abiraterone acetate, many authors questioned whether an AAWS with these new drugs exists. The purpose of this paper was to review the evidence about the classic AAWS with first-generation antiandrogen therapies and to gather initial findings on the relevance of a possible withdrawal syndrome with enzalutamide and/or abiraterone.

The AR machinery

The AR gene is located on chromosome Xq11–12 and has eight exonic sequences. Wild-type AR is a 110-kDa nuclear protein, which belongs to the steroid hormone receptor family. Four different domains are identified: the N-terminal transactivation domain (NTD), the DNA-binding domain (DBD), a hinge region and the ligand-binding domain (LBD) (Germann 2002). Many endogenous hormones can activate the AR, while some others act like antagonists (Li & Al-Azzawi 2009). However, in normal conditions, LBD binds only dihydrotestosterone (DHT) and, with lower affinity, testosterone (TST). The NTD, encoded by exon 1, is the ultimate AR activity mediator, with mechanisms that are not strictly dependent from ligand–LBD interaction. Indeed, if the NTD is preserved, C-terminal LBD deletions could result in a constitutive active receptor, whereas deletions in NTD, especially in central and 3' regions of exon 1, significantly reduce receptor activity (Simental *et al.* 1991). This is a unique characteristic not shared with other steroid hormonal receptors.

The final result of AR activation is an increase in the transcription of several genes, many involved in cell growth, proliferation and inhibition of apoptosis (Heemers & Tindall 2007).

TST and DHT are natural AR ligands (Li & Al-Azzawi 2009). In the testis, production of TST is regulated by the hypothalamus–pituitary axis (Pitteloud *et al.* 2008).

Testes secrete about 7000 µg/day of TST, while very little amount of DHT (about 69 µg/day) is directly released by the Leydig cells (Hammond *et al.* 1977). Circulating TST is mostly bound to plasma proteins, primarily to sex hormone-binding globulin (SHBG) and albumin. TST is converted into the most active androgen, DHT, by steroid 5- α -reductase (SRD5A) an enzyme with two isoforms, termed SRD5A1 and SRD5A2 (Thigpen *et al.* 1993). While SRD5A2 is the dominant isoenzyme in normal prostate tissue, increased levels of SRD5A1 are linked to CRPC progression. Moreover, in CRPC androstenedione replaces TST as the main substrate for SRD5A1, that converts androstenedione to 5 α -androstenedione, that is then converted to DHT (Chang *et al.* 2011). DHT is the most potent endogenous AR ligand in humans, showing higher affinity, greater stability and a slower rate of dissociation than TST. Its concentration in the prostate gland is 10-fold higher than that in serum, which is relevant for prostate diseases, such as benign prostatic hyperplasia and PCa (Randall 1994).

Pharmacokinetics of antiandrogens

Bicalutamide is a competitive and pure AR antagonist *in vitro* and an antiandrogen *in vivo*. Currently, it is the most commonly used antiandrogen, in combination with LH–RH analogues and, to a lesser extent, in monotherapy, because of its long half-life (about 6 days), higher potency and better tolerability when compared to flutamide (Mahler *et al.* 1998). It is usually administrated at the dose of 50 mg/day when used as part of the CAB, and at the dose of 150 mg/day when used as single agent. In laboratory animal studies, bicalutamide shows complete selective peripheral activity that has not been confirmed in humans, probably correlated to differences in the blood–brain barrier permeability (Cockshott 2004). Therefore, bicalutamide as single agent leads to an increase of LH levels and, consequently, in the TST production by testis. Bicalutamide is administered as racemate, but its *in vivo* activity is due to the R-isomer, as the S-isomer is quickly cleared and loosely binds AR and R-bicalutamide has about 30-fold less affinity compared to DHT (Gao *et al.* 2006).

First-generation antiandrogens withdrawal syndrome

For a long time, first-generation non-steroidal antiandrogens (NSAA) have represented the best available hormonal therapy for metastatic or unresectable

prostate tumors, controlling the disease and postponing chemotherapy. Subsequently, their role has been downsized by the introduction of LHRH analogues. However, bicalutamide is still widely used in the treatment of PC, as its administration increases and maximizes the efficacy of ADT. Adding an AR antagonist to androgen suppression in the CAB strategy is an effective and well-tolerated treatment of PCa that significantly prolongs the overall survival (Akaza 2011). Eventually, resistance to CAB occurs at some point, usually with a rise in PSA values. In several studies, the occurrence of resistance has been correlated to an increased number of AR copies expressed by prostatic cancer cells and to increased production of intra-tumoral androgens (Nemes *et al.* 2014). However, in a less relevant but clinically significant percentage of patients (about 10%), resistance is due to specific AR mutations. These mutations can induce a gain of function of AR and a significant change in the interaction between AR and its antagonist. Hara and coworkers have first identified two AR mutations (W741C/L) that allow PCa cell lines growth after 6–13 weeks *in vitro* exposure to bicalutamide (Hara *et al.* 2003). The study suggests that these specific mutations switch the activity of bicalutamide from antagonist to agonist. This finding was further confirmed by a structural analysis of the interaction between bicalutamide and W741L AR LBD, with a 2-fold increase in binding affinity (Bohl *et al.* 2005). W741L AR-positive tumor cells, if stimulated by bicalutamide, show a significant upregulation of the MAPK pathway compared to tumor cells carrying wild-type AR (Terakawa *et al.* 2010). Even before bicalutamide, flutamide was reported to act as an agonist for T877S and H874Y AR (Fenton *et al.* 1997). Interestingly, flutamide is still able to inhibit the W741L/C AR, demonstrating that the interaction of the antiandrogens with the AR depends on specific sequences within LBD (Urushibara *et al.* 2007). Regardless, following studies failed to demonstrate an association between AR mutations found in metastatic CRPC samples and AAWS (Hu *et al.* 2010). Flutamide and bicalutamide have been proven to have agonist properties in cells engineered to express higher AR levels (Tran *et al.* 2009). Clones with AR gene amplification are commonly induced *in vivo* by long-term antiandrogen exposure (McCrea *et al.* 2016).

As a clinical consequence, patients who develop these mutations can benefit from a suspension of antiandrogen treatment. Practically, a clinical observation time of 4–6 weeks is needed to confirm the AAWS, due to the long half-life of both antiandrogens and PSA. The AAWS has been more frequently reported in early studies,

associated with a longer progression-free survival and greater improvement in quality of life (Dupont *et al.* 1993), probably due to both the different drugs used and the development of more accurate diagnostic techniques. More recent findings suggest that AAWS can be detected in about 20% of patients after cessation of AR blockers, with a median progression-free survival of 3 months (Sartor *et al.* 2008).

Before the approval of enzalutamide and abiraterone for CRPC patients, AAWS could be used to postpone the beginning of chemotherapy in metastatic prostate cancer patients with only serological progression during CAB. However, current European guidelines do not mention AAWS as a potential treatment option (Parker *et al.* 2015), due to the availability in this setting of effective and well-tolerated new-generation hormonal therapies.

Enzalutamide withdrawal syndrome (EWS)

Enzalutamide is the first approved second-generation NSAA for the treatment of CRPC. Many studies reported that enzalutamide binds AR with greater affinity than first-generation NSAA, being 5- to 8-fold more potent than bicalutamide. Moreover, enzalutamide also inhibits AR translocation inside the cell nucleus and prevents DNA binding, acting as a DNA-binding domain antagonist (Tran *et al.* 2009). Two different phase III trials demonstrated the efficacy of enzalutamide in the treatment of CRPC, both before (Beer *et al.* 2014) and after (Scher *et al.* 2012) docetaxel use. Many different mechanisms have been associated with primary and acquired resistance to enzalutamide (McCrea *et al.* 2016). The development of aberrant truncated AR variants, such as ARV-7 and ARV-567, seems to play a central role in CRPC progression (Buttiglierio *et al.* 2015). Antonarakis and coworkers reported a significantly lower response rate in patients treated either with enzalutamide or abiraterone who expressed ARV-7 in circulating tumor DNA compared to patients without ARV-7 (0% vs 53%, $P=0.004$ for enzalutamide; 0% vs 68%, $P=0.004$ for abiraterone) (Antonarakis *et al.* 2014). Furthermore, the activation of alternative growth pathways, independent from AR signaling, along with the cross-talk between AR downstream genes and other steroidal hormone receptors and ligands are probably implicated in disease progression in patients treated with new-generation hormonal therapy (McCrea *et al.* 2016). However, like first-generation NSAA, enzalutamide resistance can also be caused by some

point mutations of the full-length AR protein (Liu *et al.* 2017). F876L AR is sufficient to induce resistance to enzalutamide *in vitro*, and its occurrence changes the activity of enzalutamide from antagonist to agonist, suggesting a possible EWS (Korpai *et al.* 2013). PCa cells stressed by long-lasting antiandrogen therapies can likely activate alternative proliferative pathways not dependent from AR signaling (Tombal 2011). AR-independent tumor clones are usually more aggressive, less differentiated and unlikely to respond to further therapies. Antiandrogens discontinuation can restore AR activity, which can suppress alternative proliferative pathways and decrease disease progression. This alternative explanation of AAWS is likely underestimated in clinical practice, as it is not followed by PSA reduction. In fact, although other signaling could regulate PSA, it is strictly related to AR activity, especially in early stage disease.

The first reports of EWS were two retrospective studies. In the first report, Rodriguez-Vida and coworkers analyzed 30 patients with metastatic CRPC treated with enzalutamide (Rodriguez-Vida *et al.* 2015). Three patients had a reduction of PSA values after enzalutamide discontinuation, although only one of them matched the criteria for classic withdrawal syndrome (PSA reduction >50%). Unfortunately, no factors were found to be adequate predictors of response. In the second study, von Klot and coworkers reported the occurrence of EWS in 31 patients whose data were collected from 6 different centers in Germany (von Klot *et al.* 2014). No PSA reduction was observed in any of the 31 patients, and authors concluded that if existent, an EWS was at least very rare for enzalutamide in patients with mCRPC after taxane-based chemotherapy and without a clinical role in this setting. This was attributed to the different pharmacodynamics of enzalutamide, but further investigations in different settings were suggested. Both these retrospective analyses included patients who had already undergone chemotherapy with docetaxel. Another case of EWS was described in a patient, beginning 40 days after enzalutamide discontinuation (Phillips 2014). These initial findings were reviewed by Mosca, who pointed out how EWS may be an existing phenomenon, especially in the early phase of CRPC (Mosca 2015). Very recently, Poole and coworkers showed a PSA decline in 5 of 72 metastatic CRPC patients who discontinued enzalutamide after disease progression; unfortunately, median EWS duration of response, until subsequent PSA progression, was only 6 weeks (Poole *et al.* 2017).

Abiraterone acetate withdrawal syndrome (AbiWS)

Abiraterone acetate is an inhibitor of the androgen synthesis, approved for the treatment of CRPC patients, both in pre-docetaxel (Ryan *et al.* 2013) and post-docetaxel (de Bono *et al.* 2011) setting. It acts as a CYP17A1 inhibitor, mainly blocking the conversion of pregnenolone and progesterone into their 17 α -hydroxy derivatives. Abiraterone acetate also has a less relevant activity as a partial AR antagonist (Yin & Hu 2014). Resistance to treatment with abiraterone acetate is associated with the same mechanisms already described for enzalutamide. Because the interaction between AR and abiraterone is not the main mechanism of action, the rationale of a possible AbiWS is not as immediate as for the direct AR blockers previously discussed. Despite that, some hypotheses have been postulated. Abiraterone acetate is usually administered in combination with prednisone, in order to avoid hypocortisolism and a consequent rise of ACTH levels (Auchus *et al.* 2014). Glucocorticoid receptor (GR) gene is one of the most upregulated genes in antiandrogen-resistant PCa and shares many target genes with AR (Arora *et al.* 2013). Therefore, prednisone may bypass AR blockade and DHT deficiency through GR. GR overexpression has already been associated with enzalutamide resistance, while its role in abiraterone resistance remains to be determined. Stopping the concomitant administration of abiraterone and prednisone may induce the decrease of AR-regulated genes transcription, mediated by GR activation. Moreover, prednisone may act as a ligand for mutated AR in a low-level androgens environment. Multiple AR mutations, most notably L701H/M/Q, have been shown to modify LBD affinity range, making molecules with similar structure able to strongly stimulate AR (Van De Wijngaart *et al.* 2010). In a recent case report, even spironolactone withdrawal has been associated with a dramatic response in a patient with metastatic CRPC (Flynn *et al.* 2017). Thereby, discontinuation of both abiraterone acetate and prednisone may have positive effects in patients who are not responding to the active therapy and bearing mutations of AR that binds prednisone as a partial agonist (Gauthier *et al.* 2012). However, other authors questioned why this phenomenon has never been described after cessation of steroids administrated for other reasons, such as during taxane-based chemotherapy (Caffo *et al.* 2013). Moreover, Caffo and Sharifi have recently speculated about steroidal abiraterone metabolites, such as Δ 4-abiraterone (D4A) and 5 α -abiraterone (5aA)

having a role in the AbiWS (Caffo & Sharifi 2016). D4A is a strong AR antagonist, whose activity is comparable to enzalutamide (Li *et al.* 2015), but it is swiftly converted to 5aA, which conversely acts as AR agonist, by steroid-5 α -reductase. Hence, high 5aA blood concentrations may facilitate cancer progression if neoplastic cells have already escaped abiraterone acetate blockade (Li *et al.* 2016). However, data from a single arm phase II study that evaluated the combination of abiraterone acetate and dutasteride did not support the hypothesis of a phase III study of abiraterone with and without dutasteride (Taplin *et al.* 2016). Finally, other mechanisms still undefined, related to direct AR-abiraterone acetate interaction, could be involved.

Regardless of underlying biological mechanism, in the last few years, AbiWS has been described in several case reports and short series of patients (Gauthier *et al.* 2012, Caffo *et al.* 2013, Witjes 2013). The first two papers described two individual patients who experienced a reduction in PSA levels that lasted at least three months after abiraterone withdrawal (Gauthier *et al.* 2012, Witjes 2013). Caffo and coworkers described a series of nineteen patients who discontinued abiraterone because of progression (Caffo *et al.* 2013). A major biochemical response, with PSA reduction $\geq$ 50%, was observed in three patients. The two cases with the longest duration of the response, 5 and 6 months, respectively, performed PET scans after 3 months from abiraterone withdrawal, showing a significant reduction of the uptake values (SUVmax) (Caffo *et al.* 2013). A retrospective analysis enrolled 218 patients who had discontinued abiraterone acetate due to disease progression (Albiges *et al.* 2013). While most patients had immediately started a new treatment after abiraterone discontinuation, 66 did not receive immediately a further treatment and were assessed for PSA changes in the weeks after abiraterone discontinuation. A decrease in PSA values was observed in 21 patients (32%), and 4 patients (6%) had a PSA reduction $>$ 50%, fitting with the definition of withdrawal

Table 1 Retrospective series for withdrawal syndrome with enzalutamide and abiraterone.

Authors (year)	Drug tested	Patients	N# withdrawal syndrome (%)
Von Klot <i>et al.</i> (2014)	Enzalutamide	31	0 (0)
Rodriguez-Vida <i>et al.</i> (2015)	Enzalutamide	30	3 (10)
Poole <i>et al.</i> (2017)	Enzalutamide	72	5 (7)
Caffo <i>et al.</i> (2013)	Abiraterone	19	3 (16)
Albiges <i>et al.</i> (2013)	Abiraterone	66	4 (6)

syndrome (Table 1). From these preliminary data, it can be concluded that, although the biological mechanisms are not yet fully elucidated, AbiWS is not a rare clinical event, and its potential role in clinical practice should be better evaluated in the near future.

Discussion

Hormonal therapy withdrawal syndrome is a complex and heterogeneous phenomenon that can be associated to multiple receptor–ligand interactions, within the biological mechanisms associated with prostate cancer growth and progression. Unfortunately, it should be stated that most patients are not benefiting from withdrawing hormonal therapy at any time of their disease. Moreover, some patients may manifest symptomatic or rapidly progressing disease, even at the beginning of the castration-resistant phase, with a possible deterioration of performance status, that should discourage any ‘wait-and-see based’ strategy and the delay of the beginning of further effective treatments. In those cases, a different effective treatment should be immediately started. Accordingly, considering the availability of new active agents that have been approved in this setting, it is quite challenging to define a space for AAWS in both treatment guidelines and clinical practice.

In addition, current research is moving forward to the early use of new-generation hormonal therapies, as in biochemical-only progression of CRPC or even in hormone-sensitive disease. For instance, data from two recent studies exploring enzalutamide in association with ADT as compared with bicalutamide plus ADT showed great promises. The TERRAIN trial, a randomized phase II study, enrolled 375 patients with asymptomatic or minimally symptomatic metastatic CRPC progressing on ADT and randomized 1:1 to enzalutamide 160mg per day plus ADT or bicalutamide 50mg per day plus ADT. Patients treated with enzalutamide showed a 9.9-month improvement in median progression-free survival (PFS) (15.7 vs 5.8 months) compared with patients in bicalutamide arm (HR: 0.44; 95% CI 0.34–0.57; $P < 0.0001$) (Shore *et al.* 2016). Another double-blind phase II study (STRIVE trial) randomized 396 men with metastatic or non-metastatic CRPC to either enzalutamide 160mg daily and ADT or bicalutamide 50mg daily and ADT; the primary endpoint was PFS. Enzalutamide significantly improved PFS (median 19.4 vs 5.7 months; HR: 0.24; 95% CI: 0.18–0.32; $P < 0.001$). Similarly, time to PSA progression, proportion of patients with $\geq 50\%$ PSA response and radiographic

PFS in metastatic patients were all improved in the enzalutamide arm (Penson *et al.* 2016).

Moreover, interesting results about the activity of abiraterone in metastatic hormone-sensitive disease have been published in 2017.

The LATITUDE trial was a placebo-controlled phase III study, that enrolled 1200 men with newly diagnosed, high-risk metastatic prostate cancer who had not previously received ADT (Fizazi *et al.* 2017). Patients were randomized to abiraterone acetate plus low-dose prednisone (5mg/day) in combination with ADT (experimental arm) or ADT alone (control arm). Notably, the experimental treatment delayed radiological disease progression by an average of 18 months and reduced the risk of death by 38%, compared with ADT alone.

Another trial, the STAMPEDE study, showed similar results (James *et al.* 2017). STAMPEDE is a randomized controlled trial with a multi-stage multi-arm platform design. The trial randomized 1917 men with high-risk locally advanced or metastatic prostate cancer to receive abiraterone acetate plus low-dose prednisone (5mg/day) in addition to ADT (experimental arm) or standard hormonal therapy alone (control arm). Adding abiraterone to ADT significantly lowered the relative risk of death by 37% and the relative risk of treatment failure by 71% compared to ADT.

The early and long-lasting selective drug pressure induced by new-generation hormonal therapies may promote the growth of clones with mutated AR that exploit these drugs as agonists.

Therefore, with the earlier use of these drugs in the near future, EWS and AbiWS could become more common. Potentially, patients with asymptomatic and slowly progressive disease could undergo a period of observation before switching to another treatment. Moreover, the activation of alternative proliferative pathways independent from AR due to molecular perturbation of AR signaling pathway can lead to resistance to second-generation hormonal therapies. Preserving AR-dominant clones over other clones could reduce disease aggressiveness, providing another interesting finding about AAWS.

The association of abiraterone and enzalutamide is supported by a strong biological rationale (Buttiglierio *et al.* 2015). This association showed a favorable safety profile in a phase II clinical trial (NCT01650194) (Efsthathiou *et al.* 2014). Mechanisms underlying EWS and AbiWS are also implicated when the combination of abiraterone and enzalutamide are concurrently administered. Therefore, patients who experience progression with the

combination may still benefit from the monotherapy, withdrawing one of the two drugs. In this scenario, AAWS may have a crucial role, avoiding an early withhold of an effective therapy.

In conclusion, some clinical reports suggest that AAWS could occur, at least in a limited number of patients, even after discontinuation of new-generation hormonal agents. Further studies are obviously needed to understand how much significant AAWS could be in the clinical practice.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Author contribution statement

Gianmarco Leone and Marcello Tucci equally contributed to the review.

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Received in final form 17 September 2017

Accepted 27 September 2017

Accepted Preprint published online 28 September 2017