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REVIEW

New considerations for ADT in advanced prostate cancer and the emerging role of GnRH antagonists

ND Shore[1], P-A Abrahamsson[2], J Anderson[3], ED Crawford[4] and P Lange[5]

Androgen deprivation therapy (ADT) is first-line treatment for metastatic prostate cancer (PCa). Gonadotrophin-releasing hormone (GnRH) agonists are the most commonly used ADT but have several theoretical physiologic disadvantages (e.g. initial testosterone surge, potential microsurges upon repeat administration). Testosterone surge delays the intended serologic endpoint of testosterone suppression and may exacerbate clinical symptoms. GnRH antagonists were developed with a view toward overcoming these potential adverse physiologic events. This review evaluates GnRH agonists and antagonists, assessing the potential future role of antagonists in PCa and strategies to minimize ADT adverse events (AEs). Evidence was identified via PubMed search (by GnRH agent and other ADT-related terms), from review article bibliographies, and authors' therapy area knowledge, with articles included by author consensus. Degarelix shows similar efficacy to a GnRH agonist in achieving and maintaining castration, with faster onset and without testosterone surge/microsurges. Phase III data showed that, in the first treatment year, degarelix displayed a lower risk of PSA failure or death (composite endpoint), lower levels of the bone marker serum alkaline phosphatase (in baseline metastatic disease), and fewer musculoskeletal AEs than the agonist leuprolide. Also, crossing over from leuprolide to degarelix after 1 year reduced the risk of PSA failure or death. ADT displays an AE spectrum which can impact quality of life as well as causing significant morbidities. Strategies to improve ADT tolerability have become increasingly important including: a holistic management approach, improved diet and exercise, more specific monitoring to detect and prevent testosterone depletion toxicities, and intermittent ADT allowing hormonal recovery between treatment periods. Clinical studies suggest possible benefits of GnRH antagonists over agonists based on different mechanisms of action. GnRH antagonists should now be considered as an alternative first-line ADT option in advanced PCa. Intermittent ADT and a holistic treatment approach are promising strategies to improve ADT tolerability.

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Keywords: androgen deprivation therapy; gonadotrophin-releasing hormone; agonists; antagonists

INTRODUCTION

Androgen deprivation therapy (ADT) is first-line treatment for advanced/metastatic prostate cancer (PCa) and recommended before, during or after definitive radiotherapy for intermediate and high-risk localized PCa.[1–3] ADT is also commonly used for short periods to shrink prostate volume in patients contemplating interstitial seed implantation of PCa,[2,4] in glands >50 g, albeit this indication does not have a US Food and Drug Administration (FDA) or European Medicines Agency (EMEA) labelled indication. ADT may be accomplished with bilateral orchiectomy or via gonadotrophin-releasing hormone (GnRH) agonists or antagonists.

GnRH agonists became the leading ADT due to the reduced psychological morbidity and almost equivalent efficacy to surgical castration.[1] However, agonists display several shortcomings including testosterone surge/microsurges.[1,5] GnRH antagonists were developed with a view toward overcoming the physiologic drawbacks of agonists.

Irrespective of how it is achieved, testosterone suppression causes adverse events (AEs), e.g. hot flushes, osteoporosis and cardiometabolic effects.[6] PSA testing has increased the proportion of PCa patients diagnosed at earlier stages. The consequent increase in ADT utilization highlights the importance of strategies to reduce AEs associated with testosterone suppression.

This review compares ADT delivered by GnRH agonists and antagonists and assesses the potential future role of GnRH antagonists in PCa therapy. Novel strategies to minimize the AE risk of testosterone reduction are also explored.

METHODS

A PubMed search was conducted using the search terms 'abarelix' [title], 'degarelix' [title], 'cetrorelix' [title], 'ozarelix' [title], 'teverelix' [title], 'acycline' [title], to identify published studies on GnRH antagonists for PCa therapy. PubMed searches were also conducted using the search terms 'intermittent androgen deprivation therapy' [title]; 'androgen deprivation therapy' [title] AND 'prostate cancer' [title] (limit: reviews); and 'androgen deprivation therapy' AND 'prostate cancer' AND 'metabolic' OR 'cardiovascular' OR 'bone health' (limit: reviews). In addition, these references were supplemented by publications identified from the 'more like this' search option on PubMed, bibliographies of review articles and the authors' personal knowledge of this therapy area. The articles identified were scrutinized and those publications considered most relevant to a discussion of a comparison of ADT delivered by GnRH agonists and

[1]Carolina Urologic Research Center, Myrtle Beach, SC, USA; [2]Department of Urology, Malmö-Lund University Hospital, Malmö, Sweden; [3]Department of Urology, Royal Hallamshire Hospital, Sheffield, UK; [4]Department of Urology, University of Colorado at Denver, Denver, CO, USA and [5]Institute for Prostate Cancer Research, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA, USA. Correspondence: Dr ND Shore, Atlantic Urology Clinics, 823 82nd PKWY, Myrtle Beach, South Carolina 29572, USA.
E-mail: nshore@grandstrandurology.com
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antagonists, the potential future role of GnRH antagonists in PCa therapy, and novel strategies to minimize the AE risk of testosterone reduction, were included in the review.

GnRH AGONISTS AND ANTAGONISTS

Mechanism of action

GnRH, secreted in pulses from the hypothalamus, stimulates pituitary release of luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH subsequently stimulates testosterone secretion, predominantly by the testes (Figure 1).[8,9]

GnRH agonists and antagonists exhibit different mechanisms of action. Agonists bind to GnRH receptors and produce an initial intense stimulation. This causes marked increases in LH, FSH and testosterone. Sustained pituitary overstimulation will eventually down-regulate/desensitize GnRH receptors with a consequent decrease in hormone levels.[10] In contrast, antagonists block receptors, immediately stopping LH secretion, producing rapid testosterone suppression without the initial LH and testosterone surge.[11]

The overall effect of ADT on hormone levels in PCa differs between treatments (Table 1). Orchiectomy reduces testosterone and dihydrotestosterone (DHT) but is accompanied by significant rises in LH and FSH.[15,16] In contrast, GnRH agonists cause an initial surge in LH, FSH, testosterone and DHT; over time these hormones are suppressed.[11,17] However, FSH gradually rises during GnRH agonist treatment and FSH 'escapes' occur.[11,18] With GnRH antagonists there is a rapid and sustained suppression in LH, testosterone, DHT[12,19] and FSH.[12,20]

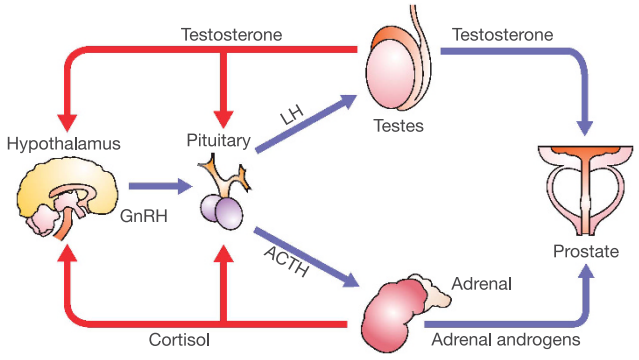

Figure 1. Endocrine control of the prostate gland. ACTH, adrenocorticotropic hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone. Reproduced from Damber *et al.*[7] with permission from Informa Healthcare.

Table 1. Effects of androgen deprivation therapies (ADT) on hormone levels[8,10–20]

ADT	*Hormone*			
	Testosterone	*Dihydrotestosterone*	*Luteinizing hormone*	*Follicle stimulating hormone*
Orchiectomy	↓	↓	↑	↑
GnRH agonist	↑↓	↑↓	↑↓	↑↓↑
GnRH antagonist	↓	↓	↓	↓

Abbreviation: GnRH, gonadotrophin-releasing hormone.
The first arrow indicates initial effects while the second and third arrows indicate secondary and tertiary effects, respectively.

Pharmacological profiles

These distinct modes of action produce different biochemical effects (Table 2). The initial agonist-induced testosterone surge can exacerbate clinical symptoms in advanced PCa[21] and delay the therapeutic effect (agonists generally suppress testosterone to <0.5 ng/ml (<1.7 nmol/l) within 3–4 weeks). Indeed, an appreciable proportion of patients ($\sim$5–17%) receiving GnRH agonists fail to achieve castrate testosterone $\leqslant 0.5$ ng/ml.[22] Testosterone microsurges associated with repeat injections also occur with agonists.[11,23] In a study with goserelin, microsurges (testosterone surges above a castration threshold of 18.5 ng/dl (0.185 ng/ml) after $\geqslant 1$ repeat injections) occurred in 17.7–27% of patients.[5] The clinical implications of microsurges are currently unclear.

Loss of GnRH receptor sensitivity during long-term agonist therapy can allow renewed testosterone production manifesting as late breakthrough testosterone escapes.[22] In 73 patients with non-metastatic PCa receiving agonists (38.4% also received bicalutamide), duration of androgen-independent progression-free survival (PFS) was correlated to the extent of testosterone breakthrough escape.[24] Mean PFS was significantly lower in patients with breakthrough testosterone >0.32 ng/ml versus those not experiencing breakthrough escape (88 versus 137 months, $P<0.003$).

GnRH antagonists achieve castration faster than agonists[11,25] and may offer better testosterone control, in terms of the absence of initial testosterone surge or subsequent microsurges.[11] Long-term testosterone control has been suggested to reduce mortality risk among patients with metastatic disease.[26] In 129 patients with metastatic PCa receiving a GnRH agonist, those with high testosterone at 6 months had a 1.33-fold increase in mortality risk.

GnRH antagonists cause profound and persistent FSH suppression[11,20] compared with partial FSH suppression with agonists.[27–29] The therapeutic advantage of persistent FSH suppression with antagonists is not fully understood. However, several studies have linked FSH with PCa. Thus, FSH stimulates PCa cell growth *in vitro*.[30] FSH receptors occur on prostate tumors[31] and the surface of tumor blood vessels[32] and are expressed at higher levels on prostate versus normal tissue.[33] Also, FSH signaling may contribute to progression of castration-resistant PCa.[34] Elevated FSH may also contribute to increased bone loss during perimenopause by promoting development of osteoclast precursor cells; FSH promotes RANK (Receptor Activator of Nuclear Factor κB) expression on CD14+ cells, indicating the acquisition of osteoclast precursor cell characteristics.[35] The exact significance of FSH is still being defined. Two studies investigated the GnRH antagonist, abarelix, in androgen-independent metastatic PCa progressing after orchiectomy[36] or GnRH agonists.[37] There were no PSA responses but these studies showed that PSA reduction could be achieved, especially in those who had previously received orchiectomy and who had the highest baseline FSH.[38]

GnRH ANTAGONIST DEVELOPMENT

Abarelix, the first antagonist available clinically in PCa, may have caused an associated histamine release, resulting in systemic anaphylactoid-like reactions.[39] The immediate-onset systemic allergic reactions led to a detailed risk management program. The manufacturer withdrew abarelix from the US market for commercial reasons. It is currently available in Germany and launch in other European countries is underway.[40] The third-generation GnRH antagonist degarelix was synthetically modified with a view toward reducing histamine-releasing activity. Degarelix displayed weak histamine-releasing properties and the lowest propensity for histamine release among GnRH antagonists tested

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Table 2. Comparison of pharmacological profiles of GnRH agonists and antagonists[10,11]

GnRH agonist (e.g., leuprolide)	*GnRH antagonist (e.g., degarelix)*
Slow onset of testosterone suppression	Rapid onset of testosterone suppression
Onset of effect delayed by 14–21 days	Fast fall in LH, FSH and testosterone
Initial testosterone surge	No testosterone surge
May cause clinical flare	No clinical flare
Testosterone microsurges	No testosterone microsurges
Partial FSH suppression	Profound and persistent FSH suppression

Abbreviations: FSH, follicle stimulating hormone; GnRH, gonadotrophin-releasing hormone; LH, luteinizing hormone.

in animal studies[41] and a human skin model.[42] Furthermore, no systemic anaphylactic reactions were observed during the clinical development of degarelix in patients with PCa.[11,12,43]

Degarelix is the only GnRH antagonist with a low risk of histamine release currently available for clinical use in PCa in the US; it is also available in other parts of North America, Japan and most European countries.

CLINICAL DATA FOR THE GnRH ANTAGONIST DEGARELIX

Efficacy

Data from two 1-year dose-finding trials[12,43] identified the most effective degarelix doses (240 mg initiation; 80 or 160 mg maintenance) and these were studied further in a large phase III trial.

Phase III data. A pivotal phase III trial (CS21) showed degarelix was non-inferior to leuprolide in suppressing testosterone to $\leqslant$0.5 ng/ml over 1 year.[11] Patients ($n=610$) with histologically confirmed PCa (all stages), for whom ADT was indicated, were randomized to degarelix (240 mg for 1 month then 80 mg ($n=207$) or 160 mg ($n=202$) monthly) or leuprolide (7.5 mg/month ($n=201$)). Anti-androgen was available as flare protection in the leuprolide group at the investigator's discretion; 11% of patients in the leuprolide arm received concomitant anti-androgen (bicalutamide).

Testosterone suppression $\leqslant$0.5 ng/ml at all monthly measurements from Days 28–364 was achieved by 97.2% of the degarelix 240/80 mg group and 96.4% of the leuprolide group. Degarelix decreased testosterone and PSA significantly faster than leuprolide. By Day 3, castrate testosterone levels were achieved in 96.1% of patients receiving degarelix 240/80 mg. In contrast, there was a 65% increase in testosterone at Day 3 in patients receiving leuprolide. After 14 days, median PSA had declined by 64% with degarelix 240/80 mg versus 18% with leuprolide. Testosterone surge (increase $\geqslant$15% from baseline on any 2 days during the first 2 weeks) occurred in 80% of patients with leuprolide versus 0% with degarelix. In the week following the ninth injection, 4% of patients ($n=8$) receiving leuprolide had testosterone microsurges (increases $>$0.25 ng/ml) versus 0% with degarelix. Rapid and sustained FSH suppression also occurred with degarelix. In contrast, leuprolide caused an initial increase in FSH, and the overall reduction in FSH was less than with degarelix (Figure 2).

Concomitant anti-androgens can reduce clinical flare but do not completely abolish the risk.[1] In a study in patients receiving GnRH agonist/anti-androgen, clinical flare effects such as bone pain appeared/worsened in 29% of patients.[44] In the phase III degarelix trial, in patients receiving agonist plus anti-androgen, PSA reduction was greater than with agonist alone but similar to that with degarelix.[11] Nonsteroidal anti-androgens are associated with AEs such as gynaecomastia and breast pain while steroidal agents (e.g. cyptoterone acetate) cause loss of libido and erectile

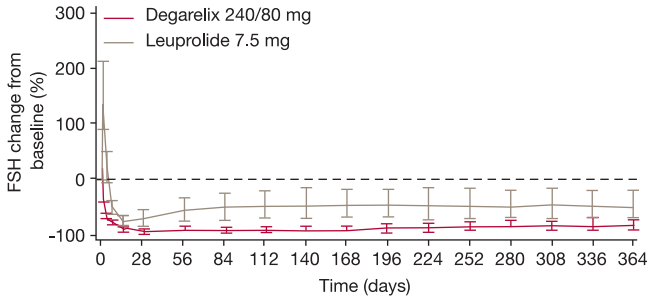

Figure 2. Rapid and sustained follicle stimulating hormone (FSH) suppression in the phase III CS21 trial. Adapted from Klotz *et al.*[11] with permission from John Wiley and Sons.

dysfunction (and cardiovascular and hepatotoxicity).[1,45] GnRH antagonists avoid potential anti-androgen AEs, as well as possible issues with compliance and additional cost considerations. Hence, GnRH antagonist monotherapy offers an effective alternative to combined GnRH agonist/anti-androgen therapy.

Effect on PSA control and alkaline phosphatase. Secondary analyses of the phase III study suggest that degarelix 240/80 mg offers improved PSA control versus leuprolide. Patients receiving degarelix 240/80 mg had a significantly lower risk of PSA failure or death (composite endpoint) versus leuprolide ($P=0.05$) in the first year.[46] PSA failure occurred mainly in patients with advanced disease and exclusively in those with baseline PSA $>$20 ng/ml. Moreover, patients with baseline PSA $>$20 ng/ml also had a significantly longer time to PSA failure with degarelix ($P=0.04$).

In patients with baseline metastatic disease, baseline serum alkaline phosphatase (S-ALP) levels were high reflecting the presence of skeletal metastases. In these patients, after 1 year, S-ALP reduction was significantly greater with degarelix 240/80 mg than with leuprolide (mean S-ALP levels at day 364 were 96 and 179 IU/l, respectively ($P=0.014$), for degarelix and leuprolide).[47] After initial peaks in both groups, patients receiving degarelix 240/80 mg maintained S-ALP suppression throughout the study and avoided the late increases in S-ALP (which might suggest therapy failure) observed with leuprolide. This suggests that degarelix might offer better S-ALP control than leuprolide and might prolong control of skeletal metastases in metastatic disease compared with GnRH agonists, over a 1-year period; however, the clinical relevance of better S-ALP control remains to be fully determined.[47]

Long-term data. There are currently no long-term data on survival differences between therapy with degarelix and GnRH agonists. However, a 5-year extension (CS21a) to the pivotal trial is ongoing to investigate long-term safety and efficacy of degarelix (Figure 3). At the end of CS21 (after 1 year), patients receiving degarelix could continue treatment while those receiving leuprolide could cross over to degarelix.[48] The risk of PSA failure or death decreased in patients switching from leuprolide to degarelix, whereas the risk remained constant in patients continuing with degarelix (Figure 4).[48,49] At a median follow-up of 27.5 months, PSA PFS hazard rates had reduced significantly—risk of progression in one year was more than halved from 0.20 events/year in the first year to 0.08 events/year following the switch from leuprolide to degarelix ($P=0.003$). For patients continuing to receive degarelix 240/80 mg, corresponding hazard rates were 0.11 and 0.14 events/year ($P=0.464$), indicating no significant change and a consistent effect of degarelix over time. The same hazard rate pattern occurred in patients with baseline PSA $>$20 ng/ml. Finally, the time for 25% of patients with baseline PSA $>$20 ng/ml to experience PSA failure or death was also significantly longer with degarelix (514 versus 303 days; $P=0.01$;[49] Figure 5).

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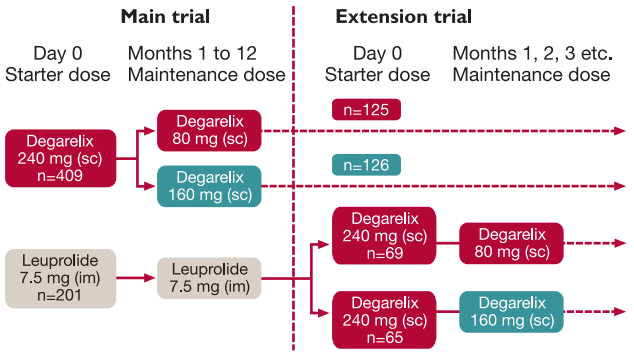

Figure 3. Study design for pivotal phase III trial (CS21) and its open-label extension (CS21a).

Tolerability

Degarelix was well tolerated in Phase II/III studies, displaying an AE profile consistent with androgen deprivation,[11,12,43] with no systemic allergic reactions reported.

In CS21, overall tolerability was similar for degarelix and leuprolide.[11] Injection-site reactions were more frequent with degarelix 240/80 mg (35%) than with leuprolide (<1%), predominantly occurring after the first injection. This may reflect different administration routes (subcutaneous degarelix versus intramuscular leuprolide) and a higher injection volume for degarelix. Local injection-site reactions were previously reported with GnRH agonists when given subcutaneously.[51] Chills were also more frequent with degarelix (4% for pooled degarelix 240/80 mg and 240/160 mg groups versus 0% with leuprolide, $P<0.01$) whereas urinary tract infections were more common with leuprolide (9% with leuprolide versus 3% for pooled degarelix 240/80 mg and 240/160 mg groups, $P<0.01$). The frequency of musculoskeletal AEs was also greater with leuprolide (26%) versus degarelix (17%) 240/80 mg ($P=0.001$), during the 1-year trial.[52]

In the long-term extension trial (CS21a), the overall incidence of AEs was similar in patients continuing on degarelix and those who crossed over from leuprolide to degarelix, and decreased as the study progressed. The occurrence of first-time musculoskeletal and connective tissue AEs (more frequent with leuprolide during the first year in CS21) was similar between patients continuing on degarelix (17%) and those switching from leuprolide to degarelix (20%; $P=0.532$).[48]

The FDA recently highlighted an increased risk of diabetes, heart attack, stroke and sudden death with GnRH agonists based on an Agency review of published studies; warnings of such risks must now be added to GnRH agonist labels.[53] In contrast, most (but not all) studies appear to indicate that orchiectomy is not associated with greater risk of cardiovascular events.[54–56] Such observations may suggest that, for different types of ADT, the potential for cardiovascular risk may vary.

A recent analysis of safety data from CS21 showed degarelix to have an overall cardiovascular safety profile comparable to leuprolide.[57] After 1 year, mean change in Fridericia's correction of QT interval was similar with degarelix 240/80 mg (3.5%) and leuprolide (3.5%). Marked prolongation of the QTc interval was infrequent (⩽1%) in both groups. Rates of new ischemic heart disease or arrhythmias were not significantly different between groups.

A pooled analysis of >1700 men treated with degarelix showed that established cardiovascular disease was associated with a greater risk of cardiovascular events.[58] Furthermore, cardiovascular event risk was affected by modifiable risk factors (e.g. obesity and alcohol consumption), but not by degarelix dose or testosterone level. This suggests that cardiovascular risk with degarelix may be driven by normal aging.

CLINICAL DATA FOR THE GnRH ANTAGONIST ABARELIX

Phase III data

Three randomized phase III studies with abarelix in advanced PCa have been reported.[59–61] US studies compared abarelix with leuprolide alone[59] or with bicalutamide[60] over 3 and 6 months, respectively, while a 48-week European trial compared abarelix with goserelin/bicalutamide.[61] In these trials, abarelix and comparator groups were equivalent in achieving and maintaining castration for 3[59,61] or 6 months.[60] Furthermore, abarelix produced more rapid testosterone suppression to castrate levels, without the testosterone surge associated with GnRH agonists. In the US trials, PSA suppression was similar for abarelix versus GnRH agonist + antiandrogen[60] but was initially more rapid with abarelix when compared with GnRH agonist monotherapy.[59] In both US trials, abarelix rapidly decreased LH and FSH.[59,60]

In 81 symptomatic patients with advanced PCa, by Day 85 abarelix had produced an 88% objective response rate and 90% of patients experienced improvement in pain score and/or analgesic use, urinary obstruction, urinary catheter removal, hydronephrosis, and/or azotemia.[62]

Long-term efficacy. In the 6-month US trial, achievement and maintenance of castrate testosterone with abarelix was equivalent to leuprolide/bicalutamide after 24 weeks.[60] However, in the European trial, escape from castration was more frequent with abarelix versus goserelin/bicalutamide (22 versus 8%); also time to escape from castration was significantly shorter with abarelix ($P=0.007$).[39] The abarelix package insert warned that, in some patients, effectiveness of testosterone suppression to castrate levels diminishes with continued dosing and effectiveness beyond 12 months had not been established (http://patient.cancerconsultants.com/druginserts/abarelix.pdf). In studies of up to 48 weeks, waning of castration rates after 24 weeks appeared to be more frequent with abarelix than active controls.[25]

A recent study evaluated ADT with abarelix for 12 weeks followed by a GnRH agonist; one aim was to establish whether antagonist therapy eliminates the initial testosterone surge seen after agonist administration. During the first agonist injection, there was a small but transient increase in testosterone from 0.17 to 0.373 ng/ml.[63] Whilst these levels are less than traditional castrate levels (0.50 ng/ml), it has been suggested more recently that levels should be reduced to <0.20 ng/ml[64] Interestingly, in a preclinical study of the effects of switching from a GnRH antagonist to an agonist, there was a transient rise in testosterone levels after withdrawal of the antagonist.[65] In the abarelix switch study, microsurges were reported in some patients after the second agonist injection.[63]

Tolerability

In phase III trials, abarelix displayed a generally comparable safety prolife and similar overall incidence of AEs to GnRH agonist ± antiandrogen.[39,59,60] However, overall data show that 1.1% (15/1397) of PCa patients receiving abarelix (predominantly without advanced symptomatic disease) experienced immediate-onset systemic allergic reactions.[25] Of patients with advanced symptomatic PCa, 3.7% (3/81) experienced such allergic reactions. The cumulative risk of these reactions increased with treatment duration (http://patient.cancerconsultants.com/druginserts/abarelix.pdf). The previously established low-frequency, immediate-onset allergic reactions were not observed in a more recent, relatively short-duration study.[63]

HOLISTIC THERAPY

Castration in PCa is usually associated with bone loss[66] which may also be influenced by factors such as obesity, age and exercise. Moreover, ADT is associated with increased fracture risk.[67] Bone

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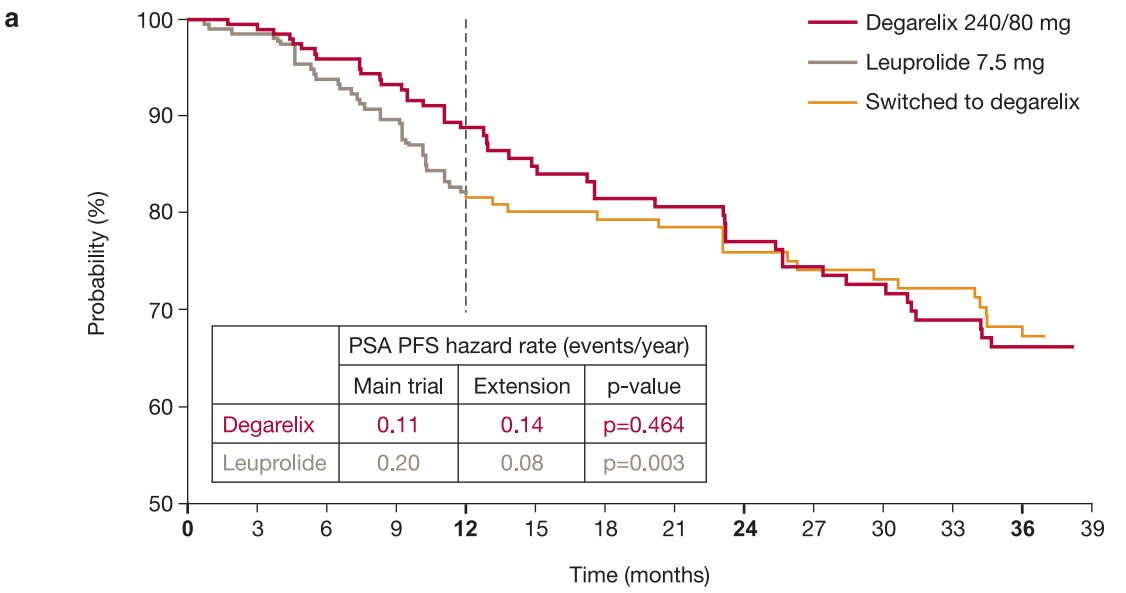
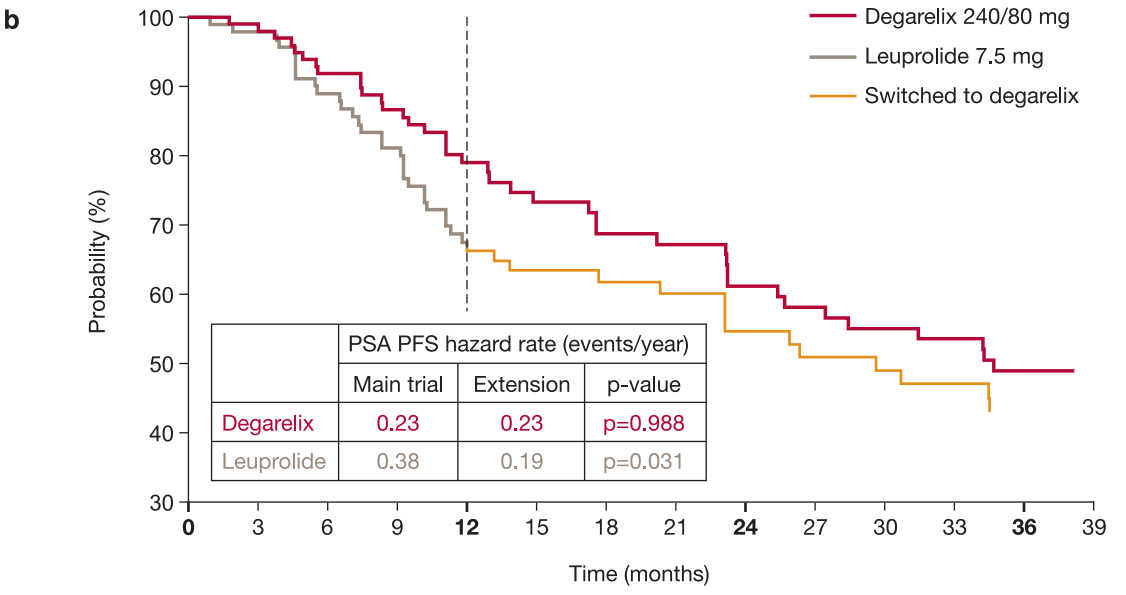


Time (days)	*0*	*84*	*168*	*252*	*336*	*420*	*504*	*588*	*672*	*756*	*840*	*924*	*1008*	*1092*	*1176*
Number of patients at risk															
Degarelix	207	200	187	176	162	109	101	93	91	87	83	79	75	71	67
Leuprolide	201	193	182	174	157	110	102	98	93	85	81	78	74	68	66



Time (days)	*0*	*84*	*168*	*252*	*336*	*420*	*504*	*588*	*672*	*756*	*840*	*924*	*1008*	*1092*	*1176*
Number of patients at risk															
Degarelix	100	97	91	84	77	53	50	45	44	40	37	36	35	32	31
Leuprolide	93	90	81	75	63	43	40	37	35	29	27	26	23	23	21

Figure 4. PSA progression-free survival probability in the extension phase of a phase III study for (**a**) all patients and (**b**) patients with baseline PSA >20 ng/ml. Reproduced from Crawford *et al.*[48] with permission from Elsevier. PFS, progression-free survival.

fractures are of particular concern, given their negative correlation with overall survival (OS) in men with PCa.[68]

ADT has also been linked to metabolic complications. ADT can increase weight and fat body mass, and decrease lean body mass and muscle size,[69] and also insulin sensitivity.[70] ADT can also increase total and low-density lipoprotein cholesterol, and triglycerides.[71] Pooled data from three trials showed that short-term ADT affects serum lipids and hemoglobin A1C (there were

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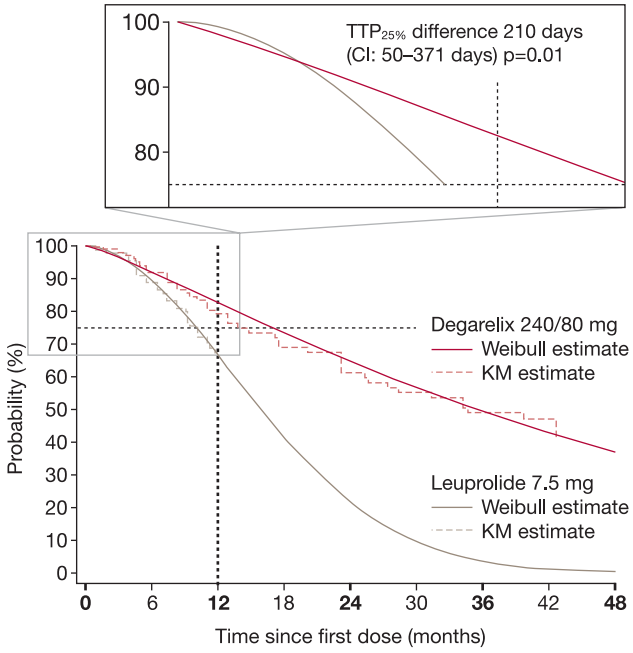

Figure 5. Time for 25% of patients with baseline PSA >20 ng/ml to experience PSA failure or death. Reproduced from Boccon-Gibod *et al*.[50] with permission from Sage Publications.

significant increases in total cholesterol, triglyceride and high density lipoprotein-cholesterol with leuprolide or abarelix but not with leuprolide/bicalutamide).[72] In all three ADT groups, hemoglobin A1C increased from baseline to Day 85 only. Metabolic changes associated with ADT may have significant consequences for cardiovascular health. Thus, ADT has been associated with increased risk of incident diabetes, coronary heart disease, acute myocardial infarction, and sudden cardiac death.[55] However, in a pooled analysis of randomized trials in unfavorable-risk PCa, ADT use was not associated with an increased risk of cardiovascular death.[73]

By assessing patients' susceptibility to such effects, a holistic treatment programme can be tailored to maximise ADT efficacy, while protecting against AEs.[74] Patients receiving ADT should be counselled to help them recognize, prevent and manage AEs and encourage a healthy lifestyle including a healthy diet and regular exercise.[75]

Measures to promote bone health include weight-bearing (resistance) exercise, smoking cessation, vitamin D and calcium supplementation and moderate alcohol consumption.[76,77] Bisphosphonates (which increase bone mineral density (BMD) in patients treated with ADT[6]) should be considered in patients with fractures or BMD T scores $\leqslant -2.5$.[78] Also, denosumab, a monoclonal antibody against receptor activator of nuclear factor-κB ligand, has increased BMD and reduced the incidence of new vertebral fractures among men receiving ADT for non-metastatic PCa.[79] Clinicians should carefully assess fracture risk (e.g., using the World Health Organization fracture risk assessment tool; FRAX) and BMD should be monitored at regular intervals.[76,80]

When making treatment decisions about ADT, physicians and patients should consider the metabolic AEs and risk of diabetes and cardiovascular disease. Clinicians should educate patients about these risks and adopt risk reduction strategies. This includes following existing guidelines for lifestyle modifications, screening for pre-diabetes/diabetes and management of lipids.[81] Patients in whom ADT is initiated should be monitored with periodic follow-up evaluation including assessment of blood pressure, lipid profile and glucose level. Patients with cardiac disease should receive appropriate secondary preventive measures recommended by existing guidelines.[54]

Indeed, European Association of Urology (EAU) guidelines on PCa recommend encouraging patients to adopt lifestyle changes (e.g., increased physical activity, smoking cessation, decreased alcohol consumption, healthy eating, and normalization of body mass index) before starting long-term ADT.[1]

INTERMITTENT THERAPY

Intermittent ADT (IAD) is also a possible alternative for some patients to minimize ADT AEs while maintaining anti-tumour efficacy.[82] During IAD, active treatment periods are separated by periods without treatment. On-treatment periods normally last 6–9 months or until a PSA nadir <4 ng/ml.[83] Off-treatment periods are more variable, with treatment reinstated if PSA increases. Optimal thresholds for stopping/resuming ADT are empirical and the best candidates for IAD have not been completely defined (EAU guidelines consider these are 'probably patients with locally advanced or relapsing disease, provided a perfect response is obtained'). Treatment is stopped only if patients are well-informed and compliant and there is no clinical progression (a clear PSA response: PSA <4 ng/ml in metastatic disease, or 0.5 ng/ml in relapsing disease).[1] After treatment ceases, there should be a clinical examination every 3–6 months (the more advanced the disease, the closer the follow-up) and PSA should be monitored. Treatment is resumed if there is either clinical progression or a PSA value above a predetermined, empirically fixed threshold (usually 4–10 ng/ml in non-metastatic or 10–15 ng/ml in metastatic patients).[1] A systematic review of data from 19 phase II and of interim data from 8 phase III trials, found that the PSA threshold for stopping treatment was usually $\leqslant$4 ng/ml, and treatment was restarted generally at >10 or >20 ng/ml.[84] Also, a meta-analysis ($n = 1446$ patients) showed that restarting treatment at PSA <15 ng/ml was associated with improved survival compared with restarting at PSA levels $\geqslant$15 ng/ml.[85]

Phase II data show that IAD is a feasible approach.[86] During off-treatment periods, quality of life (QOL) improves and patients experience reduced treatment-related morbidity. Phase III IAD data are limited. However, a study in >600 patients with locally advanced/metastatic PCa showed comparable efficacy for IAD and continuous androgen deprivation (CAD) with no difference in time to progression and OS.[87] Several AEs were significantly reduced with IAD versus CAD including hot flushes, gynaecomastia, headaches, and skin complaints. Better sexual function was also reported with IAD.

The comparable efficacy of IAD and CAD was supported by a recent long-term randomized phase III trial which found similar OS with IAD and CAD in 1386 men with rising PSA after radical radiotherapy.[88] Median OS was 8.8 versus 9.1 years on IAD and CAD, respectively ($P = 0.009$ for non-inferiority). Time to hormone-refractory state was significantly improved with IAD ($P = 0.024$). Hot flushes were reduced with IAD, but there were no between-group differences in other AEs.

Moreover, a systematic review concluded that IAD is at least as effective as CAD while showing tolerability and QOL advantages, especially recovery of sexual potency.[84] The UK National Institute for Health and Clinical Excellence recommends that IAD be offered as a first-line hormonal therapy option to men with newly diagnosed or relapsing metastatic cancer, provided they are aware of the therapy's unproven status.[89] Furthermore, EAU guidelines conclude that IAD is already widely offered to patients with PCa in various clinical settings and its status should no longer be regarded as investigational.[1]

Nevertheless, results from ongoing Phase III studies together with further research may clarify issues such as selection of the

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most appropriate patients to receive IAD, optimal thresholds for stopping/resuming therapy and ADT agents most suitable for IAD.

There appears to be a paradox between the need to maintain low testosterone levels during ADT and allowing testosterone levels to rise/recover during the off-treatment phase of IAD. It is not yet clear how these two issues can be reconciled and further studies are needed to fully explain this. However, it may be related to the type of patient being treated, in terms of tumour characteristics and disease stage.

SUMMARY

ADT is the mainstay of treatment for advanced PCa and, until recently, largely comprised GnRH agonists. However, GnRH antagonists may offer potential advantages over agonist therapy related to their mechanism of action. Thus, the GnRH antagonist degarelix suppresses testosterone and PSA more rapidly with no initial testosterone surge or subsequent microsurges, and no need for concomitant anti-androgens. Avoiding a testosterone surge may help avoid cancer stimulation and worsening of clinical status, as well as providing more rapid relief of cancer-related symptoms. Faster castration onset may benefit patients presenting with critical clinical problems such as cord compression, impending long bone fracture or ureteric obstruction,[90] and may offer physiological advantages for patients receiving neoadjuvant and intermittent ADT. While degarelix is currently only available as a 1-month formulation, GnRH agonists do offer the convenience of longer-term (e.g. 3–6 month) depot formulations, which are less frequently administered.

Other differentiating features of degarelix observed were, during the first treatment year, a lower risk of PSA failure or death, lower S-ALP levels in metastatic disease, and fewer musculoskeletal AEs than the agonist leuprolide. PSA recurrence often precedes clinically detectable recurrence by years, and effective PSA control is associated with improved OS.[91–93] Sustained S-ALP control with degarelix may suggest stabilization of bone metastases in comparison to patients receiving GnRH agonists for metastatic disease although the clinical relevance of better S-ALP control remains to be fully determined. Degarelix has also maintained effective testosterone and PSA suppression for >3 years. Together these data appear to support degarelix use as a first-line ADT option.

Although the only GnRH antagonists currently clinically available are degarelix and abarelix, others have been investigated for use in PCa. These include: acyline, which has suppressed testosterone in healthy volunteers;[94,95] teverelix which in preliminary phase II data (although not yet available in a peer-reviewed publication) appeared to show testosterone suppression to castrate levels;[96] and ozarelix, which induced apoptosis in hormone-refractory androgen receptor-negative PCa cells.[97] Cetrorelix, used in infertility to prevent premature ovulation, has shown improvements in symptoms in phase I/II studies in advanced PCa patients;[98,99] however, it is no longer in development for PCa.

ADT is associated with a range of AEs, e.g. bone loss, metabolic and cardiovascular complications, etc. A variety of strategies should be considered to effectively manage these effects, in particular, a more holistic treatment approach. This should include counselling on diet and exercise to promote general health with regular patient monitoring in terms of bone density, metabolic and cardiovascular parameters, etc. In addition, IAD offers an alternative option for some patients to minimize ADT AEs; allowing hormonal recovery between treatment periods may improve QOL. Results to date are promising, with IAD providing efficacy comparable to CAD with improved tolerability.

In conclusion, for many years, GnRH agonists have been the standard of care in hormonal therapy for the management of advanced PCa. More recently, GnRH antagonists have been developed as a new class of ADT. Clinical experience with these agents, and in particular with the most extensively studied antagonist, degarelix, suggests possible benefits over GnRH agonists. Thus, GnRH antagonists should be considered as a first-line therapeutic for ADT in advanced PCa management.

CONFLICT OF INTEREST

Neal D Shore: Consultant: Ferring, Sanofi, Watson, Astellas, Dendreon, Janssen, Amgen. Per-Anders Abrahamsson: no financial interest or conflicts with regard to the compounds included in this manuscript. John Anderson: previously received honoraria from Ferring Pharmaceuticals. E David Crawford: is an advisor to Ferring Pharmaceuticals, GlaxoSmithKline, Centocor and Sanofi-Aventis, and has been a meeting participant for Aureon. Paul Lange: no conflicts of interest.

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