Management of Advanced Prostate Cancer With Relugolix: Illustrative Case Scenarios From an Advanced Practice Provider Perspective

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Abstract

Prostate cancer is the second most common cause of cancer-related mortality among men in the United States, with an estimated 34,700 deaths annually. Androgen deprivation therapy (ADT) is the cornerstone of advanced prostate cancer therapy, and injectable luteinizing hormone-releasing hormone (LHRH) agonists have served as the most commonly used ADT for over 30 years. Relugolix, a first-in-class, once-daily, oral gonadotropin-releasing hormone (GnRH) antagonist, was developed to address some of the limitations of available ADT therapies. Herein, we present two hypothetical case reports via an advanced practice provider (APP) perspective that reflect prototypical examples of patients with advanced localized disease not suitable for surgery or newly diagnosed hormone-sensitive metastatic disease treated with relugolix. The cases presented are meant to be instructional and within the scope of the current approved prescribing information for all medications mentioned. Best practices from an APP perspective are shared.

CASE STUDY 1: ADVANCED LOCALIZED DISEASE

These patient cases are fictional and do not represent events or a response from an actual patient. The authors developed these fictional cases for educational purposes only.

Diagnosis

Fred is a 70-year-old man with a history of localized prostate cancer, previously managed with radical prostatectomy and adjuvant radiation 4 years ago. He presented with a testosterone level of 402 ng/dL and a prostate-specific antigen (PSA) of 12.9 ng/mL, with a PSA doubling time of 4 months. Fred also had diabetes (A1C = 6.2) and hypertension

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(135–150/80–90), he was overweight (body mass index [BMI]: 28), and had hyperlipidemia (i.e., high cholesterol; a total cholesterol of 240 mg/dL, triglycerides of 220 mg/dL, high-density lipoprotein [HDL] of 40 mg/dL, and low-density lipoprotein [LDL] of 180 mg/dL). He was taking metformin, lisinopril, and simvastatin, and had a Gleason score of 7 (4+3) from the initial biopsy. Upon clinical workup, laboratory tests revealed a hemoglobin level of 16 g/mL, hematocrit 45%, white blood cell (WBC) count of 7,800 mm^3 with normal differential, platelets 250,000/µL, blood urea nitrogen 14 mg/dL, creatinine 1.1, and normal alkaline phosphatase and liver function tests.

Recent evaluation with CT, MRI, and bone scan revealed a 1.9-cm prostate bed lesion. Given these findings, a biopsy of the lesion was done, showing recurrent Gleason 4+4=8 prostate adenocarcinoma. Since Fred had prior prostatectomy and radiotherapy, and with biopsy-proven recurrence and PSA doubling time of less than 6 months, systemic treatment was recommended. Fred had a very busy work schedule and had no regular exercise routine. The medical team noted that with the risk of heart disease due to comorbid diabetes, hypertension, and hyperlipidemia, oral relugolix may be a good option due to fewer major adverse cardiovascular events (MACE) observed in the pivotal phase III study relative to leuprolide. He also stated his personal preference for daily oral vs. injection every 3 months. After a shared decision-making conversation with his clinical team, Fred opted for ADT with relugolix, with lifestyle modifications (diet and exercise) recommended and medications for comorbidities unchanged.

Treatment

Based on diagnosis, medical history, and relevant guidelines, Fred was prescribed relugolix. The approved dose and administration were utilized: treatment was initiated with a relugolix loading dose of 360 mg on the first day and treatment continued with a 120-mg dose taken orally once daily at approximately the same time each day with or without food. The clinical pharmacist reviewed Fred's medication list to advise if there are any contraindicated medications. The treating APP discussed the most commonly occurring adverse events. The most common adverse reactions (≥ 10%) and laboratory abnormalities (≥ 15%) in the relugolix prostate cancer phase III trial were hot flush, increased glucose, increased triglycerides, musculoskeletal pain, decreased hemoglobin, increased alanine aminotransferase (ALT), fatigue, increased aspartate aminotransferase (AST), constipation, and diarrhea (Myovant Sciences, 2023). The APP advised Fred to inform the clinical team of any change in medications, as relugolix may prolong QT interval and advised on contraception methods if the patient is sexually active with women of reproductive age, per the guidance provided in the relugolix prescribing information (Myovant Sciences, 2023).

The APP gave recommendations to Fred on how to best manage adverse events and provided counseling on managing these adverse events if they occur. To mitigate fatigue, the APP advised him to exercise 30 minutes per day, 5 days per week with an emphasis on resistance training, which can mitigate muscle loss and bone density loss from ADT (Piraux et al., 2020). Given the history of cardiovascular disease risk factors (diabetes, hypertension, overweight, hyperlipidemia), the APP notified and advised Fred's primary care provider and cardiologist to closely monitor those risk factors. The APP discussed decreased libido and erectile dysfunction adverse events. The APP offered referral to a dietitian for dietary modifications to help with ADT metabolic adverse events. The dual x-ray absorptiometry (DEXA) scan performed for ADT baseline showed normal bone density and will be repeated every 2 years. Calcium and vitamin D3 supplementation daily was recommended per National Comprehensive Cancer Network Guidelines (NCCN, 2022). Over-the-counter analgesics were recommended for possible joint/muscle pain adverse events.

Follow-Up and Outcome

After 48 weeks, Fred was still receiving relugolix for treatment. Early in the course of treatment, Fred experienced hot flash and fatigue. The APP reinforced with Fred the management of hot

flash and discussed how to mitigate fatigue. Fred was prescribed venlafaxine for intolerable hot flash and instructed to titrate up to 75 mg qhs (ie, every night at bedtime; although venlafaxine is not approved for treatment of hot flash, data have shown that it can reduce hot flash; Johnson & Carroll, 2011). Available options for acupuncture and integrative medicine consult for evaluation were also discussed with Fred along with their limitations.

Fred had satisfactory compliance and tolerance for treatment. The first time his testosterone was measured, Fred's level decreased to 18 ng/dL after 1 month of treatment and was rechecked every 3 months. His PSA was also reexamined approximately every 3 months and has been decreasing, with the latest being a nadir at 0.15 ng/mL. Imaging examinations including MRI pelvis, contrast-enhanced CT (chest/abdomen) scan, and bone scans found decreased tumor volume, no disease progression, and no lymphadenopathy or distant metastasis. Fred will undergo imaging studies after 6 months and then annually if PSA is controlled and no progression noted.

CASE STUDY 2: NEWLY-DIAGNOSED HORMONE-SENSITIVE METASTATIC DISEASE

Diagnosis

Patrick is a 66-year-old man with no prior history of prostate cancer who presented with fatigue, left hip bone pain, and trouble urinating. His primary care provider performed a PSA with a result of 48.7 ng/mL. He was then referred to Urology for workup. Patrick had no other major risk factors for prostate cancer, was not taking any concomitant medications, and his past medical history was unremarkable. A prostate biopsy was performed. Initial imaging (chest x-ray, bone scan, and abdominal/pelvic CT scan) revealed nodal and bone metastases (N1M1b, stage IVB; American Joint Committee on Cancer, 2017). Imaging and pathology indicated an adenocarcinoma with a Gleason score of 8 (4+4) involving over half of the gland and established capsule penetration, and right seminal vesicle involvement. Laboratory testing revealed a hemoglobin of 15 g/mL, hematocrit 43%, WBC count 7,500 mm^3, normal differential, platelets 250,000, blood urea nitrogen 15 mg/dL, creatinine 1.0, and normal alkaline phosphatase and liver function tests. At diagnosis, the testosterone level was 444 ng/dL. Patrick is retired and takes 30-minute walks at least three times a week.

Treatment

Patrick was evaluated by a medical oncologist. Based on his diagnosis, medical history, and relevant guidelines, Patrick was prescribed relugolix due to a patient preference for daily oral therapy. Dosing and administration were based on the approved relugolix prescribing information. Upfront therapy options in metastatic hormone sensitive prostate cancer per NCCN Guidelines were reviewed with Patrick (NCCN, 2022). These include triplet therapy with ADT + darolutamide or abiraterone/prednisone + docetaxel chemotherapy, combination therapy with ADT + an approved novel hormonal agent, and ADT alone (if the patient does not qualify for additional therapy). In this case, enzalutamide, which was one of the agents permitted to be utilized in the HERO study (Shore et al., 2020), was added 1 month after initiating relugolix.

Follow-Up and Outcome

Patrick received 48 weeks of relugolix (ongoing) and as noted above, enzalutamide was added 1 month into ADT therapy, as per standard practice at our institutions. The enzalutamide was prescribed as US Food and Drug Administration (FDA) approved, with 160 mg administered orally once daily.

Early in the course of treatment, Patrick experienced nausea, diarrhea, and fatigue. The APP reviewed diet and recommended a consultation with a nutritionist. The BRAT (bananas, rice, applesauce, and toast) diet was recommended as it includes foods that are gentle on the stomach that can help reduce nausea, vomiting and diarrhea. The BRAT diet is considered restrictive and so other options for diet were also discussed with Patrick, including avoiding high-sugar and fatty/fried foods. For management of diarrhea, the APP recommended

over-the-counter loperamide as needed. His nausea resolved with diet changes, diarrhea is well controlled with loperamide, and fatigue is ongoing but tolerable.

Patrick had satisfactory compliance for treatment. The PSA has been reexamined approximately every 3 months and thus far PSA is undetectable. After 49 weeks of treatment, testosterone levels are 34 ng/dL. Imaging examinations, as recommended by current guidelines (NCCN, 2022), including pelvic MRI, contrast-enhanced CT scan, and bone scans found no progression of prostate cancer, with the nodal metastasis resolved and bone metastases stable. He is continuing treatment with relugolix and enzalutamide.

Prostate cancer is one of the most common cancer diagnoses in men, with an estimated 288,300 new cases in the United States in 2023 (ACS, 2023). With over 34,700 deaths estimated annually, prostate cancer is the second most common cause of cancer-related mortality among men in the United States (ACS, 2023). The disease can be defined by primary tumor status, metastatic vs. nonmetastatic, prostate-specific antigen (PSA) levels (hormone sensitive vs. hormone resistant [i.e., castration-resistant]), and prior chemotherapy exposure (Scher et al., 2016; Teo et al., 2019). Prostate cancer is dependent on androgens for growth and progression, and androgen deprivation is an effective therapeutic strategy that is widely used in clinical practice (Teo et al., 2019). Disease progression signaled via rising PSA, imaging or clinical progression, despite castrate testosterone levels (< 50 ng/dL), signals transition into a castration-resistant state.

Androgen deprivation therapy (ADT) is the cornerstone of advanced prostate cancer therapy, with either luteinizing hormone-releasing hormone (LHRH) agonists or gonadotropin-releasing hormone (GnRH) antagonists utilized (Merseburger et al., 2016). Luteinizing hormone-releasing hormone agonists and GnRH antagonists suppress testosterone levels through different mechanisms (Kittai et al., 2018); agonists bind to the pituitary gland's LHRH receptor inducing a negative feedback loop, which results in excess release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), causing initial increased testosterone release, typically within 10 days. Treatment with antagonists results in an immediate decrease of FSH and LH secretion, causing an instant decrease of the testicle's testosterone production (Figure 1).

Androgen deprivation therapy is recommended as the backbone of systemic therapy or as neoadjuvant/concomitant/adjuvant therapy in combination with radiation in localized or locally advanced prostate cancers (Parker et al., 2015; Mohler et al., 2010; NCCN, 2022). While surgical orchiectomy results in permanent androgen deprivation, the vast majority of men in developed countries receive medical ADT, usually with GnRH antagonists or LHRH agonists, with the main goal of vastly reducing or eliminating testicular testosterone production (Gupta et al., 2014).

Androgen deprivation may be achieved using long-acting depot injectable LHRH agonists, such as leuprolide and goserelin, which cause long-term downregulation and desensitization of the hypothalamic-pituitary-gonadal axis (Conn & Crowley, 1994). However, LHRH agonists typically result in an initial testosterone flare due to their mechanism of action (Figure 1). The associated testosterone flare and delay of up to 4 weeks to achieve castration necessitates initial combination with antiandrogens for flare protection. The clinical testosterone flare caused by LHRH agonists may include symptoms such as bone pain, obstructive urinary symptoms or, rarely, ureteral obstruction or spinal cord compression (Wu et al., 2021; Oh et al., 2010; Conn & Crowley, 1994). In addition, testosterone recovery after stopping LHRH agonists therapy may take months or years and depends on a number of factors, including age and length of therapy.

Degarelix (Firmagon), an injectable GnRH antagonist, is approved as a depot injection for ADT. Clinical trials for degarelix demonstrate rapid testosterone suppression without an initial testosterone surge. This medication has not achieved widespread clinical utilization. Possible reasons for this low use in clinical practice include monthly

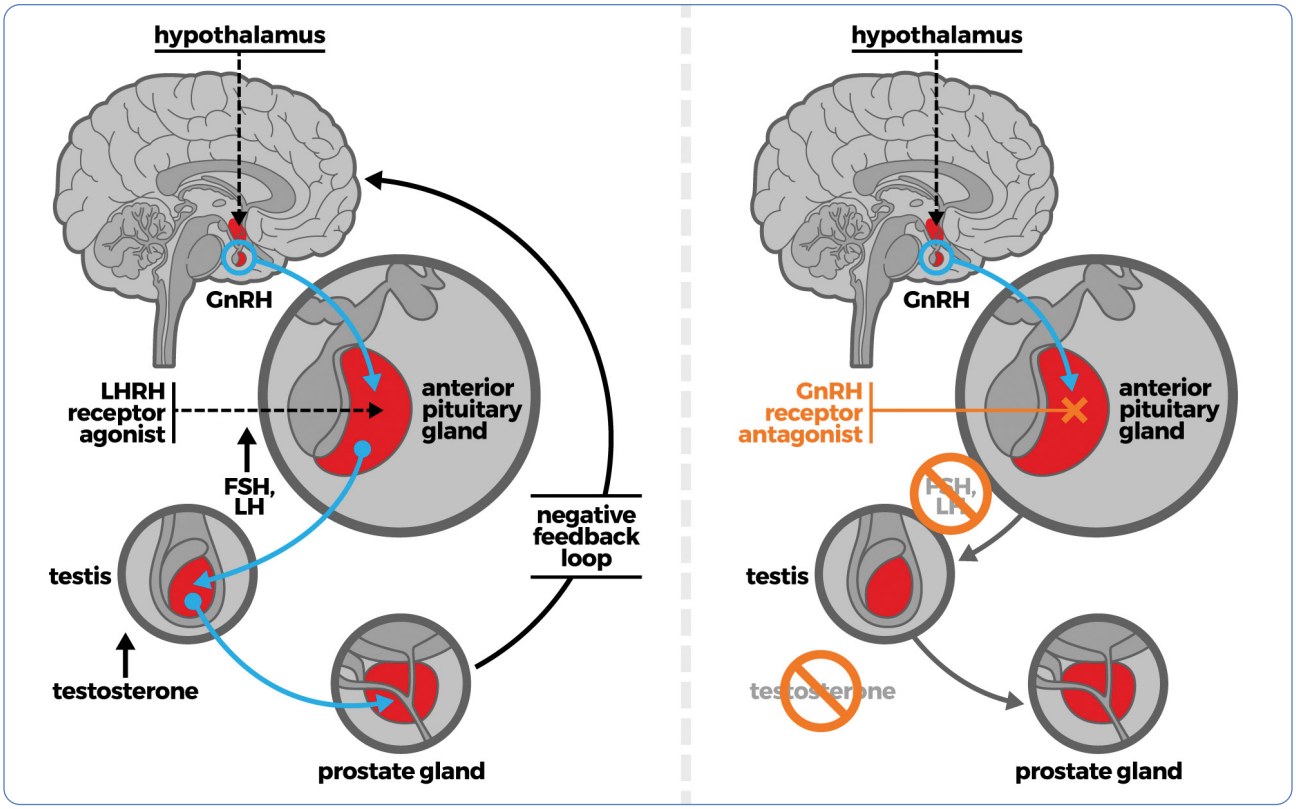

Figure 1. Mechanism of action of androgen deprivation therapy.

injections and an incidence of injection-site reactions approaching 40% (Suzuki et al., 2019; Klotz et al., 2008; Van Poppel & Klotz, 2012).

Relugolix (Orgovyx), a first-in-class, oral GnRH antagonist, was developed to address some of the limitations of available ADT therapies. In multiple phase I and phase II studies, relugolix lowered testosterone by rapidly inhibiting pituitary release of LH and FSH (Suzuki et al., 2019; MacLean et al., 2015; Dearnaley et al., 2020; Saad et al., 2016). Based on the promising results from the early phase trials, a phase III study of relugolix, the HERO study, was initiated. In this pivotal trial, relugolix demonstrated suppression of testosterone to castrate levels in 96.7% of patients from day 29 through 48 weeks, which was superior to leuprolide, and resulted in a 54% lower risk of major adverse cardiovascular events (MACE), defined as nonfatal myocardial infarction, nonfatal stroke, and death from any cause, relative to leuprolide (Shore et al., 2020). The most common adverse events observed in relugolix-treated patients were hot flash, fatigue, constipation, diarrhea, and arthralgia (Shore et al., 2020).

OPTIMIZATION OF ADT TREATMENT WITH RELUGOLIX

For patients with advanced local prostate cancer or newly diagnosed metastatic prostate cancer, like those depicted in these cases, ADT is a recommended treatment option (Mcleod, 2003; Sharifi et al., 2005; Cornford et al., 2017; NCCN, 2022). Luteinizing hormone-releasing hormone agonists, such as goserelin, histrelin, leuprolide, or triptorelin, and GnRH antagonists, such as relugolix and degarelix, are recommended ADT options based on available evidence in the literature, although individual agents have varying specific indications and recommended uses (NCCN, 2022).

The recommendation of relugolix as a treatment option for patients with advanced prostate cancer is based on data from the HERO study, which was published in the *New England Journal of Medicine* in 2020 (Shore et al., 2020). The HERO study was a global phase III trial in which 930 men with advanced prostate cancer were treated in a 2:1 ratio with oral relugolix 120 mg daily after a day 1 360-mg loading dose (N = 622) or leuprolide injections (N = 308) every 12 weeks for a total

of 48 weeks. To be eligible for the HERO study, patients needed to have evidence of biochemical or clinical relapse after primary therapy with curative intent, newly diagnosed hormone-sensitive metastatic disease, or advanced localized disease that is unlikely to be cured. In addition, men who had major cardiac events (myocardial infarction, unstable symptomatic ischemic heart disease, cerebrovascular events, or any significant cardiac condition) up to 6 months prior to enrollment were excluded. Relugolix met the primary endpoint of the HERO study and results for key secondary endpoints, including early and profound castration rates as well as testosterone recovery, demonstrating a statistically significant benefit for relugolix vs. leuprolide ($p < .001$). Castration resistance-free survival (CRFS) assessed during the 48-week treatment of relugolix was not significantly different than standard-of-care leuprolide in the subgroup of men with metastatic disease or in the overall modified intention-to-treat population (Saad et al., 2023).

Adherence to oral therapies is an important consideration when deciding between a daily oral and an injectable therapy. In the HERO study, treatment adherence with oral relugolix was > 99% and similar to that of injectable leuprolide (Shore et al., 2020). This is consistent with real-world adherence rates (between 92% and 96%) found in the literature for the novel oral androgen axis-directed therapies used for castration-resistant prostate cancer (Behl et al., 2017; Lafeuille et al., 2014).

In the HERO study, the overall incidence of adverse events was consistent across both treatment arms, with hot flash as the most common adverse event in both arms (relugolix: 54.3%; leuprolide: 51.6%; Shore et al., 2020; Table 1). As expected for an oral agent vs. an injectable, diarrhea was more common in the relugolix group than in the leuprolide cohort (12.2% vs. 6.8%, respectively). Diarrhea events were all mild to moderate, and there were no treatment withdrawals because of diarrhea. Other common adverse events

Table 1. Common Adverse Events for Relugolix

	Relugolix (*N* = 622)		Leuprolide (*N* = 308)	
	Any grade, *n* (%)	**Grades 3–4, *n* (%)**	**Any grade, *n* (%)**	**Grades 3–4, *n* (%)**
Any adverse event	578 (92.9%)	112 (18.0%)	288 (93.5%)	63 (20.5%)
Serious adverse event	76 (12.2%)	61 (9.8%)	47 (15.3%)	35 (11.4%)
Fatal adverse event	7 (1.1%)	–	9 (2.9%)	–
Major adverse cardiovascular event[a]	18 (2.9%)	8 (1.3%)	19 (6.2%)	4 (1.3%)
Without a history of MACE[b]	15 (2.8%)	–	11 (4.2%)	–
With a history of MACE[c]	3 (3.6%)	–	8 (17.8%)	–
Adverse events that occurred in > 10% of patients in either group				
Hot flash	338 (54.3%)	4 (0.6%)	159 (51.6%)	0
Fatigue	134 (21.5%)	2 (0.3%)	57 (18.5%)	0
Constipation	76 (12.2%)	0	30 (9.7%)	0
Diarrhea	76 (12.2%)	0	21 (6.8%)	0
Arthralgia	75 (12.1%)	2 (0.3%)	28 (9.1%)	0
Hypertension	49 (7.9%)	10 (1.6%)	36 (11.7%)	2 (0.6%)

Note. Adverse event grades are evaluated based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03. MedDRA Version 22.0. MACE = major adverse cardiovascular event; SMQ = standardised MedDRA query.
[a]Search criteria included Myocardial Infarction SMQ (broad), Central Nervous System Hemorrhages and Cerebrovascular Conditions SMQ (broad), and deaths due to all causes.
[b]Number of patients without a history of MACE was 538 in relugolix group and 263 in leuprolide group.
[c]Number of patients without a history of MACE was 84 in relugolix group and 45 in leuprolide group.

for relugolix (> 10%) included fatigue, constipation, and arthralgia (Table 1). During the study, the mortality rate was 1.1% in the relugolix group and 2.9% in the leuprolide group.

There was a difference in MACE (defined as nonfatal myocardial infarction, nonfatal stroke, and death from any cause) observed between the treatment groups in the HERO study (non-adjudicated prespecified analysis). After 48 weeks of treatment, the MACE incidence was 2.9% (exact 95% confidence interval [CI] = 1.7%–4.5%) in the relugolix group and 6.2% (exact 95% CI = 3.8%–9.5%) in the leuprolide group (Shore et al., 2020). Kaplan-Meier estimates of incidence rate were consistent with a 54% risk reduction (hazard ratio of 0.46, 95% CI = 0.24–0.88) in the relugolix group relative to the leuprolide group. In the subgroup of patients with a reported medical history of these events, the MACE rate on study drug treatment was 3.6% in the relugolix group compared with 17.8% in the leuprolide group, reflecting a 5.8-fold higher odds of having an event in men treated with leuprolide compared with relugolix. The HERO trial was not specifically designed or powered to show a difference in MACE; a randomized study that will answer this question is ongoing (REPLACE-CV; NCT05605964).

When selecting the ADT option that is right for an individual patient, it is important to take into account the profiles of the various ADT options. For example, the long-acting injectable LHRH agonist formulations are effective and commonly used as ADT for men with advanced prostate cancer (NCCN, 2022). However, LHRH agonists can cause an initial surge in testosterone that may result in a clinical flare, with symptoms including bone pain, obstructive urinary symptoms or, rarely, ureteral obstruction or spinal cord compression (Wu et al., 2021; Oh et al., 2010; Conn & Crowley, 1994). In addition, most guidelines recommend adding an antiandrogen for the first few weeks of treatment due to delayed testosterone suppression levels with LHRH agonists (Mcleod, 2003; Sharifi et al., 2005; Cornford et al., 2017; NCCN, 2022). Another ADT option is the GnRH antagonist, degarelix, which is approved as a depot injection for ADT. Treatment with degarelix has been shown to produce rapid testosterone suppression without an initial testosterone surge, but the need for monthly injections and an incidence of injection-site reactions approaching 40% has limited its clinical use (Suzuki et al., 2019; Klotz et al, 2008; Van Poppel & Klotz, 2012).

The role of APPs in the management of prostate cancer is essential. For APPs, it is very important to realize the benefits of ADT and also the adverse events. Advanced practice providers play a significant role in assessment, education of patients and family on prevention of complications from ADT, along with treatment selection and monitoring on treatment. The education to the patient and family should be tailored to the stage/extent of disease and it also must be provided in a clear and sensitive manner that is appropriate to the background and specific situation of the individual patient. The amount of relevant information on cancer management, including details about laboratory tests, imaging results, and surgical procedures, can often overwhelm a patient. Goals of APPs include educating the patient regarding why they need a specific test, how the tests are used, mitigating adverse events, and giving options on preventive treatments (both pharmacologic and nonpharmacologic) for potential adverse events from the cancer treatment. Managing patients on multiple treatments (e.g., ADT, chemotherapy, bone-targeted agents, etc.) will require trying to maximize appointment consolidation as well as timely management of adverse events such as electrolyte abnormalities, fatigue, hot flash, and others. The APP is in a unique and important position to make significant contributions in oncology care for their patients.

An APP should discuss risks and benefits of each treatment option with patients, ensure that the patient's own health priorities are considered in the discussion, and provide a treatment adherence plan to the patient as well as what to do in the event of a missed dose. For relugolix, current instructions for patients are that if it is less than 12 hours since missed dose, take the pill. If it has been more than 12 hours, do not take relugolix and resume with the next pill the next day (Myovant Sciences, 2023). Decision aids can be useful to help guide discussions with patients and patient decision-making (Stacey et al., 2014). Lifestyle counseling should be offered to the patient

as needed. Collaboration with multidisciplinary team members is essential, as shared decision-making improves patient satisfaction and quality of care (Will et al., 2019; Aizer et al., 2013).

STRATEGIES FOR SUCCESSFUL MANAGEMENT OF ADVERSE EVENTS

Prior to initiating therapy, the patient care team should discuss anticipated adverse events and plan for mitigation, monitoring, and management if an event occurs. As noted above, common adverse events with relugolix include hot flash, fatigue, constipation, diarrhea, and arthralgia. Patients should be made aware that ADT is also associated with some elevated risk for developing other conditions, such as osteoporosis, insulin resistance/diabetes, anxiety/depression, erectile dysfunction/loss of libido, and cardiovascular (CV) conditions (discussed further in the following section). Osteopenia/osteoporosis may occur, especially in patients with bone metastases (for example, in the second case study), which can lead to poor posture and/or bone fractures. The APP should encourage patients to exercise, quit smoking, limit alcohol intake, and educate on the importance of calcium and vitamin D supplementation. Referrals to dietitians and physiotherapists can be made as needed. Treatment options include calcium/vitamin D supplements, bisphosphonates, and receptor activator of nuclear factor kappa beta (RANKL) inhibitors (e.g., denosumab).

The APP should establish a plan for regular communication between the patient and caregiver team, including the schedule for future office visits, noting when to call the office if a patient is experiencing an adverse event, and important steps patients can take to mitigate some common adverse events. For patients who live a significant distance from the office, plans can be altered to better suit their needs. For example, phone calls or video conference calls can be used in place of an in-person meeting, when possible, to avoid frequent travel to the clinic office. The care team should use the Common Terminology Criteria for Adverse Events for assessing adverse events and compare initial (or baseline) assessments against assessments in future office visits. Table 2 provides a high-level overview of some possible management strategies for common adverse events with relugolix.

Cardiovascular Risk

Cardiovascular (CV) risk factors as well as CV disease are present in nearly 50% of the general population over 20 years of age in the United States, with prevalence increasing with age (Benjamin et al., 2019). Men with prostate cancer are likely to have CV risk factors, such as obesity, diabetes, hypertension, and hyperlipidemia (Higano, 2020).

Cardiovascular complications should be considered when optimizing treatment decisions for patients. An association between ADT and risk of CV events in men with prostate cancer has been documented (Higano, 2020). An increasing body of evidence suggests there may be a difference in the risk of CV disease between use of a LHRH agonist vs. a GnRH antagonist for ADT (Higano, 2020; Albertsen et al., 2014; Knutsson et al., 2016; Margel et al., 2019; Hopmans et al., 2014), although other studies have not shown a lower risk (Lopes et al., 2021), and most evidence is from retrospective studies. Luteinizing hormone-releasing hormone agonists are associated with increased risk of CV/MACE events, new onset diabetes, and metabolic syndrome. Prescribing information for LHRH agonists already contain warnings about increased risk of myocardial infarction, sudden cardiac death, and stroke (FDA, 2010). Overall, the available data is not conclusive. Importantly, there is a need to increase awareness of CV risk in patients with prostate cancer across the multidisciplinary health-care provider team. The priority should be focused on optimizing prostate cancer treatment for individual patients, with careful consideration of ADT modality required, as well as involvement of a cardio-oncologist or cardiologist, especially in high-risk men.

COMBINATION THERAPY AND DRUG-DRUG INTERACTIONS

In the second case study, the patient with newly diagnosed metastatic prostate cancer was prescribed combination therapy with relugolix and enzalutamide. The NCCN Guidelines (2022) for prostate cancer note that relugolix has not been adequately studied in combination with androgen receptor inhibitors such as enzalutamide, apalutamide, darolutamide, or abiraterone acetate, nor has it been studied in combination with docetaxel or cabazitaxel chemotherapy. However, in the

Table 2. Management Strategies for Common Adverse Events With Androgen Deprivation Therapy

Adverse event[a]	Signs and symptoms	Guidance for managing
Hot flash	Redness, especially in face, neck, and chest (erythematous skin); sudden feeling of heat and sometimes a red, flushed face and sweating	• Stay cool. At night, a "chill pillow" filled with water or other cooling material might help. Use fans during the day. Wear lightweight, looser-fitting clothes made with natural fibers such as cotton • Try deep, slow abdominal breathing (6 to 8 breaths per minute). Practice deep breathing for 15 minutes in the morning, 15 minutes in the evening, and when a hot flash starts • Acupuncture • Other treatments may help provide relief such as: » Low-dose depression drugs like venlafaxine[b] » Gabapentin, an antiseizure drug
Asthenia/ fatigue	Severely overtired; whole-body tiredness, tired legs, tired eyes, malaise	• For fatigue, exercise daily. Walking, swimming, bicycling, and dancing are all good choices. Drink plenty of fluids, eat a healthy diet, and exercise regularly (30 minutes per day, 5 days per week with an emphasis on resistance training) • Other treatment options include stimulants
Diarrhea/ constipation	Diarrhea: frequent, loose, watery stools and belly pain. Constipation: Fewer than three stools a week, lumpy or hard stools, and/or straining to have bowel movements	• For diarrhea and constipation, consider over-the-counter medications and recommend avoiding trigger foods • HCPs should withhold treatment for patients with severe symptoms until improving • Refer for dietitian/nutrition consult
Joint stiffness/ arthralgia	Aching and sore joints; tenderness, swelling, or stiffness in or around a joint	• Consider over-the-counter analgesics or other pain relievers

Note. HCP = health-care provider. Information from Johnson & Carroll (2011); Pandya et al. (2005); Terrie (2016).
[a]Consider intermittent ADT in patients who cannot tolerate symptoms of continuous therapy. Note that relugolix is not approved for intermittent therapy.
[b]Venlafaxine is not approved for the management of menopausal hot flashes.

HERO study, enzalutamide and/or docetaxel were used in combination with relugolix in 17 (3%) and 8 (1%) patients, respectively, with similar testosterone suppression and safety profile for patients who received enzalutamide/docetaxel relative to patients on relugolix alone (Shore, 2020; George et al., 2021). Patients on combination treatment had more adverse events, likely reflecting more advanced disease. A phase I, three-part, open-label, parallel-cohort study evaluating relugolix in combination with abiraterone acetate, apalutamide, or docetaxel in men with advanced prostate cancer is ongoing (NCT04666129).

Combination therapy is commonly prescribed in advanced prostate cancer (Etheridge et al., 2019). Androgen deprivation therapy combined with other agents lead to improved outcomes, including ADT combinations with docetaxel, enzalutamide, and abiraterone in various stages of prostate cancer (Sweeney et al., 2015; Fizazi et al., 2015; James et al., 2016; James et al., 2017; Sternberg et al., 2020; Hussain et al., 2018; Beer et al., 2014; Vale et al., 2016; Davis et al., 2022). A summary of drug-drug interactions for relugolix and potential concomitant prostate cancer drugs can be found in Table 3. Synergies and drug-drug interactions for key therapies for advanced prostate cancer are important to understand. Pharmacokinetic drug interactions for relugolix and various potential concomitant drugs used in the treatment of advanced prostate cancer can be extracted from existing prescribing information. Relugolix is not expected to cause clinically meaningful changes in exposure with concomitant use of abiraterone, docetaxel, darolutamide, or enzalutamide. There are no known interactions among relugolix and abiraterone, docetaxel, and darolutamide based on in vitro and clinical data. Combination therapy with apalutamide requires a dose adjustment for relugolix. Apalutamide is a combined P-glycoprotein (P-gp) and strong cytochrome P450, family 3, subfamily A (CYP3A) inducer (92% decrease in midazolam exposure and 30% decrease in fexofenadine exposure; Janssen Pharmaceutical Companies, 2023). The relugolix

Table 3. Drug-Drug Interactions for Relugolix and Concomitant Drugs

Concomitant drug (route of administration)	Clinically meaningful effects on concomitant drugs or clearance pathways	Other metabolism or transporter pathways affected (in vitro data)	Dose adjustment required for concomitant drug	Relugolix dose adjustment recommendation with concomitant drug
Abiraterone (oral)	Inhibitor of CYP2D6 and CYP2C8	OATP1B1 inhibition	No	No
Docetaxel (intravenous)	None reported	None reported	No	No
Apalutamide (oral)	Strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9. Inducer of P-gp, BCRP, and OATP1B1	OCT2, OAT3, and MATE inhibition	No	Yes[a]
Darolutamide (oral)	Inhibitor of BCRP, OATP1B1, and OATP1B3 transporters. No clinically relevant interaction with dabigatran (P-gp substrate)	None reported	No	No
Enzalutamide (oral)	Strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer	P-gp and BCRP inhibition	No	No

Note. Janssen Biotech, Inc. (2021); Sanofi-aventis (2020); Bayer (2023); Astellas Pharma Inc. (2023); Janssen Pharmaceutical Companies (2023); Myovant Sciences (2023).
[a]For combined P-gp and strong CYP3A inducers like apalutamide, the relugolix prescribing information recommends to avoid coadministration. If coadministration with apalutamide is unavoidable, increase the relugolix dose to 240 mg once daily.

prescribing information recommends increasing the relugolix dose to 240 mg daily if given concomitantly with a combination of a strong CYP3A inducer and P-gp inducer (Myovant Sciences, 2023). A complete medication review of a patient's current medications is always recommended to identify any drug interactions.

It is important to emphasize again that the cases presented in this article are hypothetical and meant to be illustrative for educational purposes only. These case studies also only reflect two patient experiences out of a large number of possible patient case scenarios. This information presented is within the scope of the current approved prescribing information for all medications mentioned unless otherwise noted. Finally, as noted previously, experience with relugolix within a combination regimen is limited in the pivotal studies. However, there were some patients within the HERO study that were given combination therapy, and there are ongoing studies with relugolix and concomitant prostate cancer medications that will further our understanding of the risks and benefits of relugolix combination therapy.

CONCLUSIONS

Advanced practice providers play a key role in the management of men with advanced prostate cancer. For men with CV risk eligible for ADT, APPs should consider the full profile of ADT options, as CV disease is common for men with prostate cancer, and CV safety profiles potentially differ among the available agents. Utilization of ADT should also involve thoughtful consideration of other risks, including osteoporosis and diabetes. An open line of communication with regularly scheduled touch points should be established with the patient and caregiver. Shared decision-making with the relevant multidisciplinary team is critical for optimal patient care. The oral GnRH antagonist relugolix has demonstrated sustained testosterone suppression superior to that of leuprolide with a lower risk of MACE events and may be a suitable option for men with advanced prostate cancer.

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Disclosure

The authors have no conflicts of interest to disclose.

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