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**Commentary**

# Relugolix in Clinical Practice: The Best Route for All?

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## Abstract

Androgen deprivation therapy (ADT) has been a mainstay of prostate cancer treatment for decades. Relugolix was FDA-approved in 2020 and is currently the only ADT option via an oral route. While the opportunity to use an oral medication for this indication has some advantages, a balanced discussion is required to understand in what clinical settings this agent truly has benefit over long-acting injectable formulations of ADT. Furthermore, patient preference, compliance, financial toxicity, and perhaps most importantly, pharmacologic characteristics must be considered.

## Introduction

Relugolix is an oral gonadotropin-releasing hormone (GnRH) antagonist indicated for the treatment of patients with advanced prostate cancer.[1] As the only oral androgen deprivation therapy (ADT) option, relugolix provides an alternate route of administration compared to the long-acting injectable agents which include degarelix (GnRH antagonist) and GnRH agonists (eg, goserelin, leuprolide, triptorelin). Relugolix is a once-daily oral option with rapid testosterone suppression and recovery, but these characteristics must be weighed carefully when the treatment is being considered in practice. The clinical implications of the drug's pharmacokinetics and patient compliance should be considered when determining its role in the treatment of prostate cancer.

## Testosterone Suppression and Recovery

The primary pharmacologic differences between GnRH agonists and antagonists are the onset of action and the testosterone flare which are both related to their innate impact on the hypothalamic–pituitary–gonadal axis. Testosterone suppression is typically achieved within days of GnRH antagonist administration, and this trend is maintained with relugolix. A phase III trial evaluated testosterone suppression after administration of relugolix in patients with advanced prostate cancer and found castration levels (<50 ng/dL) were achieved in 56.0% of patients at 4 days, and 98.7% of patients at 15 days.[2] Similarly, Klotz et al reported a rapid decrease in testosterone with degarelix; 96.1% of patients achieved castration levels at 3 days.[3] In contrast, GnRH agonists produce an initial testosterone flare and ultimately a delayed suppression with no patients achieving castration levels at 3 or 4 days after administration.[2,3] While the agonist-associated flare may be of clinical significance in patients with metastatic prostate cancer (eg, bone pain), a negative impact has yet to be demonstrated in patients earlier in their disease course including patients with non-metastatic disease or only PET-positive PSA recurrence. Furthermore, the indolent nature of prostate cancer suggests the extended onset period with agonists would unlikely impact outcomes in most scenarios. For patients with metastatic disease who require immediate testosterone suppression with a GnRH antagonist, the literature suggests a subsequent transition to a GnRH agonist for sustained castration may be considered.[4]

One of the benefits of relugolix is rapid testosterone recovery following treatment discontinuation. The HERO trial reported a near-immediate rise in mean serum testosterone levels, whereas testosterone recovery was delayed after leuprolide cessation and occurred in less than 5% of patients at 90 days.[2] However, there is no evidence to support this attribute delivers a clinically relevant advantage in patients receiving intermittent or short course ADT. Furthermore, the impact of a shorter duration of testosterone suppression in patients scheduled to receive ADT for a finite period is largely unknown. Additional comparative studies are required in the curative setting to assess outcomes. One study suggests a short time to testosterone recovery may be associated with an increased risk of prostate cancer-specific mortality.[5] For patients with recurrent disease detectable by PSA alone and/or PSMA-based imaging (with negative CT and TC99 bone scan), ADT is often used on an intermittent basis, but it should be noted that the use of ADT in this setting has not been demonstrated to improve survival. Thus, if an oral ADT is preferred for a quality-of-life benefit, it may be appropriate to ask why ADT is being used whatsoever in such patients without clear clinical benefit. Furthermore, rapid testosterone recovery in patients with metastatic prostate cancer is unnecessary and unwelcome because ADT is continued indefinitely. Therefore, it becomes unclear if an oral daily medication for perhaps 5

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years or more is truly advantageous over a long-acting injectable formulation.

The quick reversal of castration levels of testosterone with relugolix may ultimately result in undesirable outcomes in real-world scenarios where nonadherence may result from financial burden, medication access, polypharmacy, and other factors. Both the phase II and III relugolix trials reported an adherence rate of greater than 98% based on patient self-reporting,[2,6] but the actual adherence rate is inevitably much lower for patients who are using the agent in standard practice. An industry-sponsored analysis assessed adherence to injectable versus oral prostate cancer therapies.[7] The authors reported 25% of injectable ADT doses were administered late (12 or more days), and 25% of oral therapies were refilled late (3 or more days). Jacobs et al evaluated adherence to oral anticancer therapies by using an electronic monitoring system, one of the most accurate methods of assessment.[8] Adherence across all oral agents was reported to be 85.6%. Advancing age, illnesses of long duration, a higher number of medications, and increasing drug costs are contributors to poor compliance.[9] In addition, it has been suggested that geriatric patients are prone to self-discontinue medications if they are asymptomatic,[10] which would be the case in the adjuvant setting or early recurrence. Serum testosterone levels may be a suitable indirect measure of relugolix adherence but would only provide insight on adherence during the days prior to the blood collection. While treatment interruptions are inevitable, delays in the administration of long-acting injectable agents are less likely to be clinically meaningful in comparison to the risk associated with relugolix.

## Cardiovascular Safety

ADT has been associated with an increased risk of cardiovascular events including atherosclerotic cardiovascular disease.[11,12] Although the precise mechanism is unknown, animal models suggest that it may be related to the destabilization and rupture of vascular plaques.[13] Notably, the impact on plaque stability was demonstrated with leuprolide but not degarelix. Based on currently available data, it is unknown whether these effects are agent specific or whether extrapolation to other therapies within the class would be appropriate. Clinical data are conflicting regarding differences in adverse cardiovascular risks between GnRH agonists and antagonists; some data suggest a higher incidence of cardiovascular events with GnRH agonists compared to antagonists,[14,15] but there is also evidence to the contrary.[16] The PRONOUNCE trial was the first international, randomized trial whose primary objective was to prospectively evaluate cardiovascular safety.[17] The study enrolled men with prostate cancer and known atherosclerotic cardiovascular disease and reported no difference in major adverse cardiovascular events (MACE) in patients receiving degarelix versus those receiving leuprolide (5.5% vs. 4.1%, respectively; $P = .53$). The HERO trial reported the incidence of MACE was 2.9% in the relugolix arm compared to 6.2% in the leuprolide arm (hazard ratio, 0.46; 95% CI, 0.25-0.88).[2] However, cardiovascular outcomes were not a predefined trial endpoint, so these data should be viewed strictly as hypothesis generating. REVELUTION is an ongoing phase IV trial investigating the mechanism of cardiovascular toxicity from ADT (NCT05320406). REVELUTION will also compare the incidence of MACE in patients enrolled on one of three treatment arms: radiation alone, radiation plus leuprolide, or radiation plus relugolix. In addition, the REPLACE-CV trial will evaluate the risk of MACE for relugolix compared with leuprolide (NCT05605964). The results of these trials are highly anticipated and could provide the necessary data to inform optimal methods of androgen suppression in patients at risk for cardiovascular events.

## Drug Interactions

As expected for oral therapy, enzyme-, and transporter-mediated drug interactions are significant with relugolix. Concurrent use of P-glycoprotein (P-gp) inhibitors and combined P-gp and CYP3A inducers should be avoided.[1] In vitro studies suggest that relugolix is an inducer of CYP3A and CYP2B6 and an inhibitor of BCRP and P-gp. Index substrate and perpetrator drugs used in drug interaction studies are not selected based on the target population, but the results of these studies should guide future investigations with therapies frequently given in the population of interest.[18] To date, targeted interaction studies with other prostate cancer therapies have yet to be completed. George and colleagues presented a subgroup analysis of patients who received concurrent anticancer agents in the HERO trial.[19] However, the number of therapies and patients included in the analysis were extremely limited; just 2.7% of patients received enzalutamide and 1.3% of patients received docetaxel concurrently with relugolix. The subgroup analysis reported similar castration rates with or without concurrent use but failed to evaluate the impact of relugolix on the safety or efficacy of enzalutamide or docetaxel. An ongoing trial (NCT04666129) will evaluate the safety and tolerability of relugolix when given in combination with abiraterone, apalutamide, or docetaxel. Until the results of these and future drug interaction studies are complete, careful consideration should be given to concurrent use.

## Patient Preferences and Cost Considerations

Although data in patients with prostate cancer are limited, patients with other conditions have indicated a preference for long-acting injectable agents over oral medications.[20] Through a medication preference questionnaire, patients have also indicated their partiality for every 3-month dosing over monthly or daily administration. On the contrary, some data suggest that patients prefer oral medications over injectable,[21,22] but medications with short dosing intervals (eg, weekly) were evaluated in these studies, and therefore, the results should not be extrapolated to drugs with a longer dosing window (eg, every 3-6 months for injectable ADT). Regardless of population-level preferences, individual patient preferences, and circumstances must always be given appropriate consideration.

Cost considerations and access to treatment must also be considered when selecting ADT. The Average Wholesale Price (AWP) of the most commonly used long-acting injectable products is significantly less compared to relugolix: leuprolide subcutaneous, $1626 (3-month injection); goserelin subcutaneous, $2636 (3-month injection); degarelix subcutaneous (3 monthly maintenance injections), $1758; relugolix oral (84 tablets for daily administration), $8254.[23] Coverage through medical versus prescription insurance plans will also influence patient out-of-pocket costs. Borrelli et al estimated the annual out-of-pocket costs for relugolix and leuprolide for Medicare patients with metastatic prostate cancer.[24] The

study found the total cost for 1 year of relugolix was $27 756 compared to $2912 with leuprolide. For Medicare patients without supplemental insurance, the estimated annual out-of-pocket costs were $3731 and $745 for relugolix and leuprolide, respectively. Financial support programs are available for commercially insured patients prescribed relugolix, which may significantly decrease out-of-pocket costs for eligible patients. However, these programs are not available to patients whose claims are reimbursed by government programs (eg, Medicare, Medicaid). Although a formal cost-effective analysis has yet to be published, the higher cost of relugolix may financially burden both the healthcare system and individual patients unless conclusive evidence emerge that demonstrates an improvement in morbidity or mortality outcomes.

## Conclusion

Relugolix represents a significant advance, because it provides the first oral ADT option for the treatment of patients with prostate cancer, yet clinicians likely require more data to understand which patients will benefit most from the oral agent compared to the long-acting, injectable form. Shared decision-making between the patient and the provider is essential. However, patients must be selected carefully as adherence and cost are significant factors. Until targeted drug interaction studies are completed with other prostate cancer medications, relugolix should primarily be considered for monotherapy administration. Furthermore, given the uncertainties surrounding the risks and benefits of an oral daily ADT, optimal relugolix trial design should include a long-acting injectable ADT comparator arm. Financial implications, adherence considerations, and limited data from completed studies with concurrent anticancer medications presently cloud the role of relugolix in clinical practice for most patients with prostate cancer, although some data are starting to emerge.[25] Carefully designed clinical trials are the best way to provide the answers needed to define its optimal clinical utility.

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## Conflict of Interest

The authors indicated no financial relationships.

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