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Platinum Opinion

Relugolix: Five Reasons Why the US Food and Drug Administration Should Have Exercised Restraint

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Relugolix (Orgovyx; Myovant Sciences), a gonadotropin-releasing hormone (GnRH) antagonist, is the first oral agent of its class approved for patients with advanced prostate cancer [1]. Approval was based in part on the HERO study (NCT03085095), a phase 3 trial that found relugolix to be noninferior and superior to leuprolide in terms of sustained testosterone suppression to castrate levels (Δ 7.9%, 95% confidence interval 4.1–11.8%; $p < 0.001$) and key secondary endpoints [2]. However, close reading of the US Food and Drug Administration (FDA) documents reveals that the agency may have accepted and been satisfied with a single-arm study showing sustained castrate testosterone levels [3]. Here we highlight five reasons why the US FDA approval of relugolix should be contingent on rigorous post-marketing trials that assess clinically meaningful endpoints.

First, the quality of the control arm was suboptimal. The HERO study randomized patients in a 2:1 fashion to receive either oral relugolix (daily) or injectable leuprolide acetate, a luteinizing hormone–releasing hormone (LHRH, also known as GnRH) agonist, every 3 mo [2]. At a minimum, the trial should have used a multiarm design. Long-acting LHRH agonists are a cornerstone of our treatment for prostate cancer. However, degarelix, an approved injectable GnRH antagonist, is a more direct and therefore appropriate comparison for relugolix. It is worth noting that the receptor interactions of LHRH agonists and GnRH antagonists differ in achieving the same pharmacological impact (ie, castration of testosterone production). LHRH agonists act by creating an initial surge in gonadotropins before eventual downregulation of testosterone to castrate levels (< 50 ng/dl) [4]. By contrast, GnRH antagonists induce immediate suppression of the hormones mentioned above. Degarelix, a once-a-month injectable GnRH antagonist, may have served as a more appropriate control arm because of the identical mechanisms of action and an opportunity to tease apart the difference in administration route (injection vs tablet).

Second, the primary endpoint serves the trial rather than its participants. Because the primary endpoint measures the sustained castration rate from day 29 (weeks 4–5) to week 48, there is a concern that the analytical window includes the tail of the LHRH agonist flare [2]. According to the FDA analysis, 17 of the 34 leuprolide failures were attributed to a noncastrate testosterone level at day 29, compared to only 4/19 in the relugolix arm. By contrast, from day 29 to 337, there were only 14 noncastrate testosterone levels in the leuprolide arm, compared to 13 in the relugolix arm [3]. Given these data, one may deduce that the mechanism of action of each drug is responsible for driving the difference observed in this study. It is also uncertain if the initial testosterone decrease with relugolix would have a long-term effect on clinical outcomes. The perceived benefit of the GnRH antagonist is only evident in the context of the testosterone level—an endpoint that is not patient-oriented—at a time point that penalizes leuprolide.

Third, we do not know if relugolix benefits patients. Patients with prostate cancer are worried about living longer, living better, and preventing metastases when considering treatment options. Given that other GnRH antagonists have failed to show a clinical benefit over leuprolide [5], it is possible that relugolix would also fail to do so. In the context of the HERO trial, the incidence of diarrhea was nearly double in the relugolix group in comparison to the leuprolide group (12.2% vs 6.8%) [2]. There is also no

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evidence of improvements in quality of life presented. In addition, randomized studies may demonstrate superiority of leuprolide versus relugolix in the real world. Changing from an injection with a long interval between administrations to a daily pill may have dubious benefits. This poses a question: without carefully curated patients, what would the regular adherence rate for relugolix be in comparison to an injection every 3 mo? As demonstrated by patient reports of transitioning to injectable antiretroviral therapy for human immunodeficiency virus, there is a sense of liberation associated with the change from regular pills to long-acting injectables, even when injection site reactions are included [6].

Fourth, the exclusion criteria may create a selection bias. According to the HERO study, patients were excluded from the trial if they were expected to undergo chemotherapy or surgical therapy within 2 mo of initiating androgen deprivation therapy [2]. In other words, patients who may have had high-volume disease were excluded (per STAMPEDE guidelines) [7]. For patients with metastatic disease, combination therapy is becoming the new standard of care. If researchers claim that a pill for androgen deprivation is integral, then relugolix must be tested in the light of the prevailing standard of care. Exclusion requirements that are too stringent will result in a trial that is less generalizable to the public. Instead, we need randomized trials that test hypotheses in representative populations without imposing irrational limitations.

Fifth, prohibition of medications in the trial criteria censors individuals with age-typical cardiovascular comorbidities. The trial design prohibited many drugs that affect cardiovascular outcomes (eg, captopril, amiodarone, and diltiazem). Researchers may justify this exclusion on the possibility of P-glycoprotein interactions, but the reality is that the prohibitions are likely to reduce the number of participants with age-related cardiovascular risk, resulting in a less representative sample. With cardiovascular events as the leading cause of death among prostate cancer patients, especially those treated with GnRH agonists, it is easy to understand that caution is warranted [2,8]. But the HERO trial leaves many unanswered questions concerning major adverse cardiovascular events (MACEs). It is plausible that much of the separation in the Kaplan-Meier curves is caused by erroneous estimates driven by clinical flare or early testosterone-mediated events. If researchers are concerned about MACEs associated with GnRH agonists, then adequately powered trials measuring survival are necessary.

Finally, if relugolix is thought to be beneficial for patients, what role could it play in clinical practice? We suggest that Myovant Sciences, the manufacturer of relugolix, conduct continuous versus intermittent strategy trials in the biochemical relapse space that are sufficiently powered to measure quality of life. The potential of relugolix to facilitate a faster testosterone rebound is one of the mechanistic advantages of the drug over leuprolide. This phenomenon may help in interrogating the quality-of-life hypothesis between continuous and intermittent androgen deprivation therapy, carving a new path in the marketplace [9].

It remains to be seen whether the HERO findings translate into clinically relevant outcomes. In the interim, trials should be designed to measure what is relevant to patients (eg, survival, quality-of-life, metastases). The HERO trial—whether one considers one arm or comparisons across arms—is insufficient for firm conclusions, and new randomized trials with patient-oriented endpoints are required to determine whether relugolix helps patients in living longer or with better quality.

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