HERO trial: A rescue from injectable androgen deprivation therapy

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SUMMARY

The HERO trial is a Phase III, multinational, open-label, randomized controlled trial comparing relugolix (oral gonadotropin-releasing hormone antagonists [GnRH] antagonist) with leuprolide (injectable luteinizing hormone-releasing hormone [LHRH] agonist) in the patients of advance carcinoma prostate (PCa).[1] The trial enrolled PCa patients who either relapsed (biochemical or clinical) after curative local treatment (n = 467) or had incurable locally advanced disease (n = 252) or newly diagnosed with hormone-sensitive metastatic disease (n = 211). Patients with major cardiovascular events within 6 months were excluded from the study. They were randomized to 2:1 ratio to get either oral relugolix (n = 622, 360 mg followed by 120 mg once daily) or injectable leuprolide (n = 308, 22.5 mg or 11.25 mg every 3 months) for 1 year. Both the arms were balanced in terms of age, geographical region, metastasis, disease category, Gleason score, performance status, and treatment received.

The primary end point was sustained castrate level of testosterone (<50 mg/dL) during the treatment period (from 29 days to 48 weeks). The secondary end points were noninferiority or superiority of relugolix over leuprolide, probability of castrate level of testosterone at day 4 and 15, the probability of prostate-specific antigen (PSA) response, and profound testosterone suppression (<20 mg/dL) at day 15 and the mean FSH level (normal 1.5–12.4 IU/L) at 6 months.

The sustained castrate level of testosterone was maintained in 96.7% and 88.8% in relugolix and leuprolide groups, respectively, from day 29 to 48 weeks. The trial showed the superiority of the new oral drug over leuprolide (P < 0.001) in terms of primary as well as all secondary end points. These were castrate level of testosterone on day 4 (56% vs. 0%), day 15 caT (98.7% vs. 12%), testosterone level <20 mg/dL on day 15 (78.4% vs 1%), PSA response at day 15 (79.4 vs. 19.8%), and FSH suppression at 6 months (1.72 IU/L vs. 5.95 IU/L).

In the leuprolide group, there was a testosterone surge at day 4, which returned to castrate level by day 29, while in relugolix, the mean testosterone decreased to 38 mg/dL on day four. Adherence to treatment was >99% in both the groups. The most common adverse event observed was hot flashes (54.3% vs. 51.6%), followed by mild-to-moderate diarrhea (12.2% vs. 6.8%) and hepatic dysfunction (1.4% vs. 1.3%) in the relugolix and leuprolide groups, respectively. The major cardiovascular events (6.2% vs. 2.9%) and fatality (2.9% vs. 1.1%) were higher in the leuprolide group. There was an early return of normal serum testosterone level (≥280 mg/dL) at 3 months in the relugolix (54%) than leuprolide (3%) group. The authors conclude that relugolix is superior over leuprolide with lesser major cardiovascular risk.

COMMENTS

Androgen deprivation therapy (ADT) is the mainstay of treatment of high risk,[2] locally advanced, biochemical recurrent, metastatic hormone-sensitive, and castrate-resistant prostate cancer. ADT in the form of bilateral orchiectomy, GnRH agonist, or antagonist is well accepted, and no studies have shown the superiority of one over other.[3] The approximate time to achieve castrate level of testosterone in >90% patients is 12 h, 3 days, and 3 weeks in bilateral orchiectomy, GnRH antagonist, and agonist treatment, respectively.[1,4] Bilateral orchiectomy is an irreversible ADT, and is recommended for patients who require lifelong androgen suppression. GnRH agonists often cause an androgen surge that may result in worsening of bone pain, obstructive LUTS, spinal cord compression, significant cardiovascular events, and rarely death.[5,6] Hence, patients with a high risk of flare and low serum testosterone level should be considered for either GnRH/LHRH antagonist or bilateral orchiectomy (only if permanent castration is warranted) according to the saturation model.[5] This includes patients with impending spinal cord compression, extensive vertebral metastasis, severe obstructive lower urinary tract symptoms, or with high cardiovascular risk. The only commercially available GnRH antagonist for treatment of PCa is Degarelix, which showed rapid (day 3 castrate level of testosterone, 96.1% vs. 0%) and sustained testosterone suppression (castrate level of testosterone

at 1 year, 97.2% vs. 96.1%) as compared to leuprolide. One strong drawback of degarelix is high injection-site reaction (40%).[7]

This Phase 3 trial with oral GnRH antagonist showed the superiority of relugolix over leuprolide and provides level-one evidence. Still, some issues remain unaddressed, that is, what are the effects of long-term treatment, is there any survival advantage, and is there any difference in quality of life and cost-effectiveness. The efficacy and safety of relugolix as compared to degarelix remains to be addressed. Apart from rapid and sustained testosterone suppression, the other advantages of relugolix are that it is well tolerated orally, with no risk of flare, no injection-site pain and reaction, without severe systemic side effects, less cardiovascular morbidity (54% lower than leuprolide), and rapid recovery of testosterone level on treatment completion or discontinuation.[1] This novel drug is still not approved by the FDA and is under review. The cost and affordability will be a matter of debate once it is commercially available. Other newer oral drugs such as abiraterone and enzalutamide have been investigated and are now commonly used for the treatment of advanced prostate cancer as an adjunct to ADT not as a substitute.

Other studies with relugolix in PCa also showed promising results. In the Phase 2 trial of relugolix versus degarelix as a neoadjuvant or adjuvant to external-beam radiotherapy in intermediate- and high-risk patients, it has been shown that treatment with oral relugolix can achieve rapid and sustained castrate level of testosterone with the same safety profile.[8] Considering the efficacy and safety of this new drug, it appears that it may play a lead in ADT in the near future.

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