Relugolix: A Novel Gonadotropin-Releasing Hormone Antagonist for Prostate Cancer

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Abstract

Androgen deprivation therapy (ADT) is currently the mainstay of treatment for advanced prostate cancer. The peptide formulations of gonadotropin-releasing hormone (GnRH) antagonists need to be given subcutaneously every month. This led to the development of an oral, nonpeptide GnRH antagonist formulation relugolix which promptly lowers the levels of testosterone, luteinizing hormone, and follicular-stimulating hormone. On December 18, 2020, the US Food and Drug Administration approved relugolix for the treatment of adult advanced prostate cancer. The recommended loading dose of 360 mg on the 1st day of treatment, followed by 120 mg once daily orally, approximately the same time each day. The maximum plasma concentration (Tmax) is obtained within 2.25 h and is metabolized to a major extent by CYP3A mediated mechanism. Hot flushes, musculoskeletal pain, and fatigue are some of its common adverse effects. High rates of testosterone suppression with a limited adverse event profile make it an ideal therapy for the treatment of advanced prostate cancer.

Keywords: Androgen deprivation therapy, degarelix, follicular-stimulating hormone, gonadotropin antagonist, luteinizing hormone

Introduction

Androgen deprivation therapy (ADT) is a commonly used treatment to achieve castrate levels of testosterone in patients diagnosed with advanced prostate cancer.[1] According to the European and American clinical practice guidelines, suggest that 4–6 months and 18–36 months of ADT benefits patients with intermediate-risk and high-risk advanced disease, respectively.[2-6] Degarelix, a gonadotropin-releasing hormone (GnRH) antagonist, was approved in 2008 for the treatment of advanced prostate cancer. The peptide antagonist was administered as a once, monthly depot injection which has an immediate onset of action; faster testosterone suppression without the risk of flare and less cardiovascular side effects.[7-9] However, degarelix is less utilized in clinical practice due to the requirement of monthly injections and undesirable injection site reactions.[10] This paved way for the search of a novel, oral GnRH antagonist. Relugolix, a highly selective nonpeptide small molecule GnRH antagonist with a molecular mass of 62.6 Da, was developed by Myovant Sciences. It was approved by the US Food and Drug Administration for the symptoms associated with uterine fibroids.[11] The drug was investigated for the treatment of prostate cancer and endometriosis-associated pain. On December 18, 2020, relugolix was approved for the treatment of adult patients with advanced prostate cancer at a loading dose of 360 mg on the 1st day of treatment, followed by 120 mg taken once daily, at approximately the same time following days.[12]

Search strategy

A systematic literature search for exploring the potential utility of relugolix was carried out using online database PubMed, Cochrane Library, Medscape, Embase, Clinical trials, International Clinical Trial Registry Platform, Google Scholar search engines from 2016 to 2020, and latest proceedings of meetings of European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), American Society for Radiation Oncology (ASTRO), Society of

Access this article online

Quick Response Code:

Website: www.jpharmacol.com

DOI: 10.4103/jpp.jpp_170_20

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How to cite this article: Babu M, Pavithran K. Relugolix: A novel gonadotropin-releasing hormone antagonist for prostate cancer. J Pharmacol Pharmacother 2021;12:26-8.

Received: 23-12-2020 **Revised:** 22-01-2021
Accepted: 26-01-2021 **Web Publication:** 05-07-2021

Urological Oncology (SUO), American Urological Association (AUA), and European Association of Urology-European Society for Radiotherapy and Oncology-International Society of Geriatric Oncology (EAU-ESTRO-SIOG). The search terms used were "relugolix," "prostate cancer," and "oral gonadotropin antagonist" as keywords for extracting the relevant abstracts and full-texts. The search was limited to papers published in English. The flow chart of our search strategy adopted for the review is depicted in Figure 1. The authors screened all the articles and abstracts. Research articles, reviews, editorials, clinical trial reports were identified and included for the review.

Mechanism of action

Relugolix, a GnRH receptor antagonist suppresses the gonadotropins, thus lowering the levels of luteinizing hormone and follicular-stimulating hormone and consequently testosterone levels by competitively binding to GnRH receptors.[13]

Pharmacology

The drug is rapidly absorbed after oral administration of the recommended loading dose of 360 mg and 120 mg dose, once daily, and the maximum plasma concentration is reached within 2.25 h (Tmax). The half-life ($t_1/_2$) of the drug is 25 h. Relugolix is a P-glycoprotein substrate. The drug is 68%–71% bound to plasma proteins and is mainly excreted in feces (81%) and urine (4.1%).[12]

Clinical trial

Relugolix was evaluated for its safety and efficacy through the HERO study (NCT03085095), a randomized, controlled, open-label study was conducted in men with advanced prostate cancer requiring at least 1 year of ADT. This trial was conducted among 934 patients for 48 weeks randomized to receive either relugolix or leuprolide. The primary endpoint was to determine medical castration rate (achieving and maintenance of serum testosterone suppression) <50 ng/dL by day 29 through 48 weeks of treatment. The secondary endpoints were to determine the castration rates of day 4 and day 15 and castration rates with testosterone <20 ng/dL at day 15. The prostate-specific antigen (PSA) levels were also found to be lowered by 65%, 83%, and 92% after 2 weeks, 4 weeks, and 3 months, respectively, after relugolix administration.[12,14] The results of the HERO study suggest that relugolix produced faster, sustained testosterone suppression without a flare effect and faster recovery of testosterone levels with a median level at 270.67 ng/dL after 90 days on discontinuation compared to leuprolide group. To prolong the survival in patients with intermediate-risk and high-risk prostate cancer, the use of external beam radiotherapy in combination with relugolix was found to produce 95% rate of sustained castration in a phase 2 trial (NCT02135445).[15]

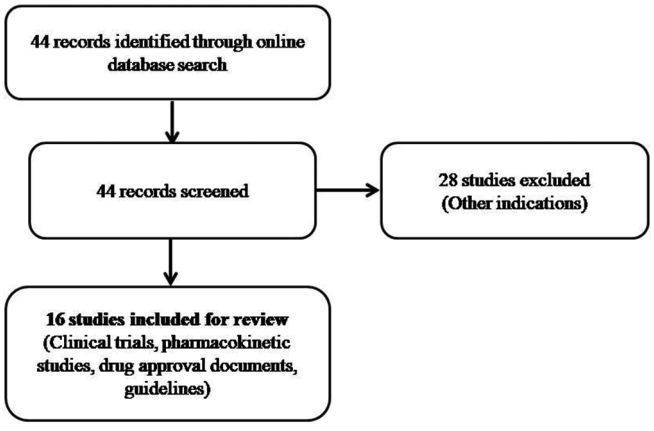

Figure 1: Representing the search strategy adopted for the review

Adverse events

Treatment-related adverse events commonly observed with relugolix were hot flushes (54%); musculoskeletal pain (30%); fatigue (26%); diarrhea; and constipation (12%). <10% of patients who received relugolix observed an increased weight; insomnia; gynecomastia; hyperhidrosis; depression; increased levels of glucose, triglycerides, aspartate aminotransferase, alanine aminotransferase and decreased libido.[12] The incidence of major adverse cardiovascular events observed in the HERO study among the relugolix group was 2.9% in comparison with the leuprolide group (6.2%) (hazard ratio, 0.46; 95% confidence interval, 0.24–0.88).[16]

Drug interactions and contraindications

Since CYP3A metabolizes relugolix, caution must be taken when the drug is co-administered with strong CYP3A inducers. If co-administration is unavoidable increase relugolix dose to 240 mg once daily. The drug may prolong the QT/QTc intervals; caution must be taken in patients with frequent electrolyte abnormalities and congestive heart failure.[12]

Conclusion

Relugolix is the first oral GnRH nonpeptide antagonist available for the treatment of prostate cancer. The drug could achieve a higher rate and magnitude of testosterone suppression with limited adverse events profile. The compliance of oral administered medication can be monitored indirectly with novel strategies developed and monitoring the testosterone and PSA levels.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Boustead G, Edwards SJ. Systematic review of early vs deferred hormonal treatment of locally advanced prostate cancer: A meta-analysis of randomized controlled trials. BJU Int 2007;99:1383-9.
2. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, Santis MD, *et al*. EAU-SIOG guidelines on prostate cancer. Part I: screening, diagnosis, and local treatment with curative intent. Eur Urol 2017;71:618-29.
3. Parker C, Castro E, Fizazi K, Heidenreich A, Ost P, Procopio G, *et al*.

Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;31:1119-34.
4. Schaeffer E, Srinivas S, Antonarakis ES, Armstrong AJ, Bekelman JE, Cheng H, *et al*. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. Ver. 2.2020. Available from: https://nccn.org. [Last accessed on 2020 Dec 21].
5. Sanda MG, Cadeddu JA, Kirkby E, Chen RC, Crispino T, Fontanarosa J, *et al*. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part I: Risk Stratification, Shared Decision Making, and Care Options. J Urol 2018;199:683-90.
6. Bekelman JE, Rumble RB, Chen RC, Pisansky TM, Finelli A, Feifer A, *et al*. Clinically Localized Prostate Cancer: ASCO Clinical Practice Guideline Endorsement of an American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology Guideline. J Clin Oncol 2018;36:3251-8.
7. Suzuki H, Uemura H, Mizokami A, Hayashi N, Miyoshi Y, Nagamori S, *et al*. Phase I trial of TAK-385 in hormone treatment-naïve Japanese patients with nonmetastatic prostate cancer. Cancer Med 2019;8:5891-902.
8. Klotz L, Boccon-Gibod L, Shore ND, Andreou C, Persson BE, Cantor P, *et al*. The efficacy and safety of degarelix: A 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. BJU Int 2008;102:1531-8.
9. Van Poppel H, Klotz L. Gonadotropin-releasing hormone: An update review of the antagonist versus agonist. Int J Urol 2012;19:594-601.
10. Lv J, Lin J. Relugolix as a promising novel oral GnRH antagonist for prostate cancer treatment. Asian J Androl 2021;23:229-30.
11. Markham A. Relugolix: First Global Approval. Drugs 2019;79:675-9.
12. Drugs @ FDA: FDA approved drugs. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-relugolix-advanced-prostate-cancer#:~:text=On%20December%2018%2C%202020%2C%20the,patients%20with%20advanced%20prostate%20cancer. [Last accessed on 2020 Dec 20; Updated 2020 Dec 18].
13. Shore ND, Saad F, Cookson MS, George DJ, Saltzstein DR, Tutrone R, *et al*. Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer. N Engl J Med 2020;382:2187-96.
14. Sachdev S, Zhang H, Hussain M. Relugolix: Early Promise for a Novel Oral Androgen Deprivation Therapy with Radiation Therapy for Prostate Cancer. Eur Urol 2020;78:193-4.
15. Dearnaley DP, Saltzstein DR, Sylvester JE, Karsh L, Mehlhaff BA, Pieczonka C, *et al*. The oral gonadotropin-releasing hormone receptor antagonist relugolix as neoadjuvant/adjuvant androgen deprivation therapy to external beam radiotherapy in patients with localized intermediate-risk Prostate cancer: A randomized, open-label, parallel-group Phase 2 trial. Eur Urol 2020;78:184-92.
16. Jena R. Relugolix - The novel oral androgen deprivation therapy for prostate cancer. Indian J Urol 2020;36:327-8.