Asian Journal of Andrology (2021) 23, 229–230
www.asiaandro.com; www.ajandrology.com

Open Access

INVITED RESEARCH HIGHLIGHT

Prostate Cancer

Relugolix as a promising novel oral GnRH antagonist for prostate cancer treatment

Jialu Lv[1], Jianqing Lin[2]

Asian Journal of Andrology (2021) **23**, 229–230; doi: 10.4103/aja.aja_77_20; published online: 24 November 2020

Continuous androgen deprivation therapy (ADT) is the mainstay of treatment for metastatic prostate cancer. Both injectable luteinizing hormone–releasing hormone (LHRH) agonists and antagonists (here LHRH interchangeable to gonadotropin-releasing hormone, GnRH) are the current standard of care for ADT in prostate cancer. The novel oral form of effective GnRH antagonist is a very promising alternative to the current landscape of ADT.

Most recently, a Phase III trial comparing oral GnRH antagonist relugolix (120 mg orally once daily) with leuprolide (injections every 3 months) in advanced prostate cancer was completed and published.[1] The primary objective of the study was to compare the ability of these agents' sustained testosterone suppression to castrate levels (<50 ng dl^{-1}) through a 48-week study period. Relugolix achieved rapid (compatible to another GnRH antagonist degarelix) castration level of testosterone that was superior to that with leuprolide, also very importantly, with a 54% lower risk of major adverse cardiovascular events (MACEs). Other side effects of relugolix were mild and expected. With final approval pending from regulatory agencies, this oral agent could be favored by both providers and patients and represent a very promising addition to the current prostate cancer treatment landscape.

[1]Ningbo University Medical School, Ningbo 315211, China; [2]The George Washington University School of Medicine and Health Sciences, Washington, DC 20037, USA.
Correspondence: Dr. J Lin (jilin@mfa.gwu.edu)
Received: 31 August 2020;
Accepted: 27 September 2020

Currently, degarelix is the only LHRH antagonist, while there are a few LHRH agonists in the USA market. These include leuprolide (in the formula of Eligard, Lupron Depot, *etc*.); goserelin (Zoladex); triptorelin (Trelstar); and histrelin (Vantas). Compared to LHRH agonists, degarelix has a pharmacological profile more closely matching orchiectomy, with an immediate onset of action and faster testosterone and prostate-specific antigen suppression, without a testosterone surge or microsurges. As a consequence, with this GnRH blocker, there is no risk of clinical flare and no need for concomitant antiandrogen flare protection. In addition to this pharmacodynamic advantage, degarelix likely has less cardiovascular side effects than LHRH agonist. A prospective Phase IIIb trial (PRONOUNCE, ClinicalTrials.gov NCT02663908) designed to compare the occurrence of MACE in patients with advanced prostate cancer and preexisting atherosclerotic cardiovascular disease receiving either a degarelix or a GnRH agonist (leuprolide) as ADT for 12 months was launched but on hold now after a feasibility analysis. However, pooled data from six Phase III prospective randomized trials that recruited 2328 men between 2005 and 2012 showed that among men with preexisting cardiovascular disease, the risk of cardiovascular events within 1 year of initiating therapy was significantly lower among men treated with a GnRH antagonist compared with those treated with a GnRH agonist (hazard ratio: 0.44; 95% confidence interval: 0.26–0.74; $P = 0.002$).[2] Overall, these cardiovascular adverse event data of degarelix match well with that of relugolix based on a recent study (**Table 1**).

Despite the advantages mentioned above, compared to LHRH agonist, degarelix is still less utilized probably due to the injection-site reaction, the requirement of monthly administration, and the less profit in practice. To seek an oral alternative seems very reasonable.

Oral medicine is one of the main methods for disease prevention and treatment because of its convenience and comfort, which leads to compliance. For patients who need treatment for many years, the oral format would be ideal. Even in the state of metastatic prostate cancer, the overall survival now could reach 9 years or 10 years thanks to a variety of therapeutic armamentaria including second-generation novel androgen receptor (AR) signaling inhibitors.[3–5] Clinical trial data support the earlier use of these agents to improve prostate cancer-specific survival. These novel AR agents are able to achieve deep androgen suppression or near-completely blocking AR which is beneficial for cardiovascular function. In theory, the longer the duration of ADT, or the deeper the androgen suppression, the higher the chance of cardiovascular adverse events. In the setting of deep androgen suppression, there is no data about difference in MACE related to the use between LHRH agonists and degarelix. We would assume that using LHRH antagonist in combination with novel AR agents maybe safer.

In summary, both injectable GnRH antagonists and agonists are the current standard of care for ADT in prostate cancer. Compared to GnRH agonist, the antagonist degarelix has less cardiovascular side effects. An oral format of antagonist relugolix is recently studied in a prospective randomized Phase III trial showing similar pharmacodynamic effects to that of degarelix. More importantly, compared to leuprolide, relugolix causes less cardiovascular adverse events. Considering its convenience, efficacy, and potentially less long-term side effects, relugolix is a very promising addition and

Table 1: Cardiovascular complications post 1 year of ADT: MACE (%) in prospective trials

Treatment	*Albertsen et al.*[2]			*Shore et al.*[1]		
	All patients, n (%; HR; P)	*No baseline CVS disease, n (%; P)*	*With a history of CVS disease, n (%; HR; P)*	*Cumulative incidence (48 weeks), % (95% CI; HR)*	*Without a history of MACE (%)*	*With a history of MACE (%)*
Degarelix (subcutaneous every 4 weeks)	62/1491 (4.1; 0.60; 0.008)	32/1028 (3.1; >0.05)	30/463 (6.5; 0.44; 0.002)			
Leuprolide or goserelin (intramuscular/subcutaneous)	57/837 (6.81)	21/592 (3.5)	36/245 (14.7)	6.2 (3.8–9.5)	4.2	17.8
Relulolix (oral daily)				2.9 (1.7–4.5; 0.46)	2.8	3.6

ADT: androgen deprivation therapy; MACE: major adverse cardiovascular events, defined as nonfatal myocardial infarction, nonfatal stroke, and death from any cause; CVS: cardiovascular; CI: confidence interval; HR: hazard ratio

likely preferable in the current androgen deprivation therapy in prostate cancer.

AUTHOR CONTRIBUTIONS

J Lv and J Lin contributed equally. Both authors reviewed the literature, drafted, read and approved the final manuscript.

COMPETING INTERESTS

Both authors declare no competing interests.

REFERENCES

1 Shore ND, Saad F, Cookson MS, George DJ, Saltzstein DR, *et al*. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. *N Engl J Med* 2020; 382: 2187–96.
2 Albertsen PC, Klotz L, Tombal B, Grady J, Olesen TK, *et al*. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. *Eur Urol* 2014; 65: 565–73.
3 Sternberg CN, Fizazi K, Saad F, Shore ND, De Giorgi U, *et al*. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. *N Engl J Med* 2020; 382: 2197–206.
4 Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, *et al*. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014; 371: 424–33.
5 Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, *et al*. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013; 368: 138–48.