Degarelix for the treatment of advanced prostate cancer compared with GnRh-Agonists: a systematic review and meta-analysis

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Received: 3 September 2015  Accepted: 8 November 2015  Published: 9 January 2016

Abstract

Background: Hormone therapy is currently the mainstay in the management of locally advanced and metastatic prostate cancer. We performed a systematic review to compare safety, efficacy and effectiveness of degarelix, a new gonadotropin-releasing hormone (GnRH) antagonist (blocker), versus gonadotropin-releasing hormone (GnRH) agonists.

Methods: MEDLINE, Web of Science and the Cochrane library were searched to identify all of the published Randomized Controlled Trials (RCTs) that used degarelix versus gonadotropin-releasing hormone agonists with or without anti-androgen therapy for the treatment of prostate cancer. We performed meta-analysis of extracted data on safety and efficacy of the target medication.

Results: Six studies were included. They involved a total of 2296 patients which were used in the meta-analysis. Follow-up times after treatment were between 12 weeks and 12 months. Three of six RCTs compared degarelix with goserelin and the others compared it with leuprolide. Meta-analysis on safety outcomes revealed that the only statistically significant difference between the degarelix treated group and GnRH agonists treated group was complication in the injection site which was higher in degarelix-treated group (OR= 46.34, 95% CI: 15.79 to 136, p<0.001). Although general mortality rate was lower in degarelix-treated group (OR= 2.06, 95% CI: 1.08 to 3.93, p<0.03); mortality due to the drug side effects was not different. Meta-analysis of efficacy data also showed that International Prostate Symptom Score (IPSS) reduction at week 12, (MD=−1.85, 95% CI: -2.97 to -0.72, p=0.001) and Testosterone reduction between day 1-28, (OR=11.58, 95% CI: 5.77 to 23.22, p<0.001) was statistically higher in degarelix-treated group. Testosterone reduction after day 28 and prostate volume reduction did not have significant difference.

Conclusion: Our meta-analysis indicates that, compared with GnRH agonists, degarelix has significantly more effects on lower urinary tract symptoms and also Prostate Specific Antigen (PSA) and testosterone reduction in the first month of the treatment. Except minor complications in the injection site like pain, erythema and swelling, there is no increase in major side effects and mortality due to degarelix. This is while the effect on testosterone and PSA after the first month of treatment is not statistically different between the two groups.

Keywords: Prostate cancer, Degarelix, Leuprolide, Goserelin, Meta-analysis, GnRH Agonists, Safety, Efficacy.

Cite this article as: Hosseini SA, Rajabi F, Akbari Sari A, Ayati M, Heidari S, Ghamary F. Degarelix for the treatment of advanced prostate cancer compared with GnRh-Agonists: a systematic review and meta-analysis. Med J Islam Repub Iran 2016 (9 January). Vol. 30:317.
Introduction
Prostate cancer is one of the most common malignant cancers around the world. According to the Cancer Statistics 2015 in USA (1), prostate, lung and bronchus, and colorectal cancers will account for about one-half of all cancer cases in men, with prostate cancer alone accounting for about one-quarter of new diagnoses. Prostate cancer is also the second cause of cancer death after lung and bronchus cancer in USA (1).

The age-standardized incidence rate of prostate cancer in IRAN is 5.1 per 100,000 person based on the data from population based cancer registries between years 1996-2000, that like other Asian countries is lower than western countries (2). This can partly be due to lack of nationwide screening program, younger age structure and quality of cancer registration system in Iran (2). Prostate cancer is the ninth cause of cancer death in IRAN (3).

After discovering the role of testosterone in prostate cancer in 1940s, suppressing testosterone level has been the main option for management of patients with prostate cancer (4). While orchiectomy is highly effective for suppressing testosterone level, the procedure is unacceptable to many patients and has now largely been replaced by different forms of medical castration, often referred to as androgen-deprivation therapy (ADT). The most common agents used for ADT are Gonadotrophin-releasing hormone (GnRH) receptor agonists that achieve the desired therapeutic goal (serum testosterone≤0.5 ng/ml) in 90–100% of patients, but only after a period of 7–21 days and an initial surge of testosterone level (4,5). This initial surge may stimulate prostate cancer cells in advanced and metastatic cases; therefore, it leads to an exacerbation of clinical symptoms (flare), including spinal cord compression, bone pain and urethral obstruction (6).

GnRH antagonists provide an alternative approach to ADT with a more direct mode of action that causes immediate blockade of GnRH receptors. These drugs produce a more rapid suppression of testosterone (and prostate-specific antigen [PSA]) without a testosterone surge and appear to provide an effective and well tolerated option for ADT of prostate cancer (7). Currently, degarelix, approved in the USA in 2008, is the most extensively studied and widely available agent in this class. Degarelix has an immediate onset of action, resulting in a rapid reduction in circulating luteinizing hormone and follicle-stimulating hormone with testosterone levels ≤0.5ng/ml achievement within 1 to 3 days after treatment (7,8).

As there are requests for using degarelix instead of GnRH agonists for management of patients with advanced prostate cancer in Iran and the need for scientific evidence to help evidence informed policy making in this field, we performed a systematic review to compare safety and efficacy of degarelix, with Gonadotropin-releasing hormone (GnRH) agonists.

Methods
We performed a systematic review of best available evidence using Cochrane Collaboration guidelines for systematic review of interventions (9). Our structured question for this review was as described in Table 1:

Relevant databases including Ovid MEDLINE (R), Scopus (by Elsevier), Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) and also Google Scholar and related websites were searched without time limitation up to 2014. Medical subject headings (MeSH) and main key words for search were ‘Prostate cancer’, ‘Androgen Deprivation Therapy’, ‘hormone therapy’, ‘GnRH agonist’, ‘GnRH antagonist’, ‘degarelix’, ‘goserelin’, ‘triptorelin’, and ‘leuprolide’. Variants of the main key words and free text terms were applied. We restricted the language to English. An example search strategy for MEDLINE has been depicted in the appendix.

The extracted articles were organized in Endnote software. After deleting the dupli-
cate articles, two reviewers independently assessed the titles and abstracts of search results and selected potentially relevant studies according to our main question (Table 1).

The studies were excluded if they either were not in English or the study designs were not Randomized Controlled trial. Disagreements were settled by examination of the full paper.

The Cochrane Collaboration’s tool for assessing risk of bias was applied to assess methodological quality and detect potential sources of bias. The scale of Jadad (10) was used to quantify the quality of included studies; this scale assesses randomization, blinding and description of withdrawals. Relevant data on study design, including patients, interventions and reported outcome measurements were recorded on an extraction form designed for this review by two reviewers. Disagreements were settled by consensus. Following agreement, the data were entered into Review Manager Software.

We performed meta-analysis using Review Manager Software (version 5) for outcome measures when the heterogeneity of data was not significant. Heterogeneity was assessed using the I² statistic, which describes the variability in effect estimate across studies that is due to differences between studies rather than random sampling error. Heterogeneity was deemed substantial if the I² analysis suggested more than 50 percent of the variability in an analysis was due to differences between trials. In such outcome measures we did qualitative analysis (0). We used random effect model for meta-analysis. The Mantel-Haenszel method was used for dichotomous outcomes and the Inverse Variance method for continuous outcomes.

### Results

The initial search yielded 581 articles, of which 96 duplicated ones were deleted.

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**Table 1. Components of structured question**

| Component | Description |
|-----------|-------------|
| Population | Patients with advanced prostate cancer; |
| Intervention | ADT using degarelix; |
| Comparator | ADT using GnRH agonists (including goserelin, leuprolin and triptorelin) with or without anti-androgen therapy; |
| Outcome | Reducing prostate volume, health related quality of life, IPSS score, general survival, reducing testosterone level, reducing PSA level, drug induced side effects; |
| Type of studies | Randomized Controlled Trials relevant to our PICO; |
From the 485 remaining papers, 421 were excluded by reviewing their titles and abstracts. Studying the full report of the 64 remaining papers led to the inclusion of 6 papers. (Fig. 1). Of course two papers (11,12) were additional analysis on data from the leuprolide-controlled pivotal Phase 3 trial of degarelix, including 610 patients treated with these agents for 12 months (13). The total number of patients was 1080. The age of patients ranged from 68 to 72 years and follow up time after treatment varied between 3 months to 14 months. Characteristics of included papers demonstrated in Tables 2 and 3.

All included studies obtained acceptable scores on Jadad scale. One paper scored 5, four papers scored 4 and the other one scored 3. The risk of bias according to the Cochrane Collaboration’s tool has been showed in Fig. 2.

### Efficacy outcomes

#### Prostate volume reduction

Three papers (14-16) reported the prostate volume after 12 weeks. These three studies involved 435 patients, 273 received degarelix and 162 received GnRH agonists. Pooled data from these studies suggested that there was no significant difference in the prostate volume reduction among the groups (MD=-0.97, 95% CI: -5.32 to 3.39, p= 0.66) within 12 weeks of ADT (Fig. 3). Heterogeneity assessment did not show significant heterogeneity (I²=38%, p=0.2).  

### IPSS score

The severity of and changes in Lower Urinary Tract Symptoms (LUTS) due to prostate cancer is assessed by the International Prostate Symptom Score (IPSS) questionnaire (17).

Three papers (14-16) reported the IPSS score after 12 weeks. These three studies involved 435 patients, 273 receiving degarelix and 162 controls. Pooled data from these studies suggested that IPSS score in degarelix treated groups is significantly lower than control groups (MD=-1.85, 95% CI: -2.97 to -0.72, p=0.001) within 12 weeks.
weeks of ADT (Fig. 4). So improving in LUTS in degarelix treated patients is obvious. Heterogeneity did not account for a significant proportion of the variability between studies ($I^2 = 0$ percent).

**Table 3. Patient characteristics**

| Paper       | Degarelix (mg) | Degarelix (mg) | Leuprorelin (mg) |
|-------------|----------------|----------------|------------------|
| Klotz       | 240/160        | 240/80         | 7.5 (n=201)      |
| (n=202)     | (n=207)        | (n=207)        |                  |
| Mean age (range), year | 72 (50-88) | 72 (51-89) | 74 (52-98)      |
| Median (range) testosterone level (IQR), ng/ml | 3.78 (2.86, 5.05) | 4.11 (3.05, 5.32) | 3.84 (2.91, 5.01) |
| Median (range) PSA level (IQR), ng/ml | 19.9 (8.2, 68) | 19.8 (9.4, 46) | 17.4 (8.4, 56)  |
| Stage of prostate cancer: number (%) | | | |
| Localized   | 59 (29)        | 69 (33)        | 63 (31)          |
| Locally advanced | 62 (31) | 64 (31) | 52 (26)        |
| Metastatic  | 41 (20)        | 37 (18)        | 47 (23)          |
| Not classifiable | 40 (20) | 37 (18) | 39 (19)        |
| Gleason score: number (%) | | | |
| 2-4         | 21 (11)        | 20 (10)        | 24 (12)          |
| 5-6         | 67 (34)        | 68 (33)        | 63 (32)          |
| 7-10        | 56 (28)        | 63 (30)        | 62 (31)          |
| Anderson    | Degarelix (n=27) | Goserelin (n=13) | |
| Mean age (range), year | 68 (53, 87) | 72 (57, 85) | |
| Median (range) testosterone level (IQR), ng/ml | 4.2 (1.1, 6.7) | 3.9 (2.7, 7.4) | |
| Median (range) PSA level (IQR), ng/ml | 54.8 (8, 1914) | 41.1 (14.6, 348) | |
| Stage of prostate cancer: number (%) | | | |
| Localized   | 4 (15)         | 0 (0)          |                  |
| Locally advanced | 4 (15) | 1 (8) | |
| Metastatic  | 10 (37)        | 4 (31)         |                  |
| Not classifiable | 9 (33) | 8 (62) | |
| Gleason score: number (%) | | | |
| 2-4         | 2 (7)          | 0 (0)          |                  |
| 5-6         | 25 (93)        | 13 (100)       |                  |
| Mean (standard error) of IPSS general score | 20.1 (1.1) | 21.1 (1.6) | |
| Mean (standard error) of IPSS QoL score | 3.6 (0.3) | 3.2 (0.5) | |
| Mean (standard error) of prostate volume, ml | 53.5 (5.5) | 50.3 (4.5) | |
| Mason       | Degarelix (n=180) | Goserelin (n=64) | |
| Mean (standard deviation) age, year | 70.6 (6.37) | 70.8 (5.96) | |
| Mean (standard deviation) testosterone level, ng/ml | 4.18 (1.72) | 4.45 (1.49) | |
| Median (range) testosterone, ng/ml | 3.92 (0.58, 11.2) | 4.42 (0.19, 8.16) | |
| Mean (standard deviation) PSA, ng/ml | 17.4 (30.1) | 13.4 (12.9) | |
| Median (range) PSA, ng/ml | 10.0 (2.5, 339) | 9.75 (2.9, 80) | |
| Stage of prostate cancer: number (%) | | | |
| Localized   | 111 (62)       | 41 (64)        |                  |
| Locally advanced | 63 (35) | 20 (31) | |
| Not classifiable | 6 (3) | 3 (5) | |
| Gleason score: number (%) | | | |
| 2-4         | 41 (23)        | 12 (19)        |                  |
| 5-6         | 97 (54)        | 42 (66)        |                  |
| 8-10        | 42 (23)        | 10 (16)        |                  |
| Mean (standard error) of IPSS general score | 9.5 (6.71) | 8.5 (6.3) | |
| Mean (standard error) of IPSS QoL score | 2.27 (1.63) | 1.94 (1.56) | |
| Mean (standard error) of prostate volume, ml | 50.9 (20.3) | 52.5 (18.8) | |
| Axcrona     | Degarelix (n=82) | Goserelin (n=97) | |
| Mean (standard deviation) age, year | 71.9 (7.71) | 73 (7.1) | |
| Mean (standard deviation) testosterone level, ng/ml | 4.25 (1.88) | 4.43 (1.64) | |
| Median (range) testosterone, ng/ml | 4.08 (0.32, 10.8) | 4.33 (0.13, 9.61) | |
| Mean (standard deviation) PSA, ng/ml | 277 (937) | 148 (438) | |
| Median (range) PSA, ng/ml | 27.8 (1.9, 6206) | 15.6 (3, 2829) | |

**Quality of life**

Quality of life related to urinary symptoms was assessed by the separate eighth IPSS question in three papers (14-16) after 12 weeks. As the heterogeneity was signifi-
cant ($I^2=78\%, p=0.01$), we did not pooled data. In two studies (15,16), more patients in degarelix treated groups reported improvement in QOL score but this difference was not statistically significant. Anderson study (18) showed that significantly more degarelix patients had improved quality of life at week 12 (85 vs. 46%; $p=0.01$).

Table 3. Cntd

| Stage of prostate cancer: number( % )    |        |        |
|------------------------------------------|--------|--------|
| Localized                                | 24 (29)| 32 (33)|
| Locally advanced                         | 30 (37)| 23 (24)|
| Metastatic                                | 22 (27)| 31 (32)|
| Not classifiable                          | 6 (7)  | 11 (11)|

Gleason score: number( % )

| 2-6     |        |        |
|---------|--------|--------|
| 7       | 24 (29)| 31 (32)|
| 8-10    | 41 (50)| 50 (52)|

Mean (standard error) of IPSS general score

|        |        |
|--------|--------|
| 14.3 (6.91) | 13.4 (7.36) |

Mean (standard error) of IPSS QoL score

|        |        |
|--------|--------|
| 2.85 (1.62) | 2.73 (1.66) |

Mean (standard error) of prostate volume, ml

|        |        |
|--------|--------|
| 54.8 (26) | 49.9 (15.5) |

Fig. 2. Included studies risk of bias based on results of critical appraisal

Fig. 3. Comparison of Prostate volume reduction between degarelix and GnRH agonist treated group
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Testosterone level reduction

Two studies (13, 18) reported the serum testosterone level ≤0.5 ng/ml between 1-28 days of treatment. These involved 364 patients, 224 receiving degarelix and 140 received GnRH agonists. Pooled data from these studies suggested that testosterone reduction ≤0.5 ng/ml is significantly more in degarelix treated group compared to control group. (OR= 11.58, 95% CI: 5.77 to 23.22, p< 0.001) in first 28 days of ADT (Fig. 5). Heterogeneity did not account for a significant proportion of the variability between studies (I² = 0 percent).

Three papers (13,15,18) reported the serum testosterone level ≤0.5 ng/ml after 28 days. These studies involved 663 patients, 400 receiving degarelix and 263 received GnRH agonists. Pooled data from these studies suggested that although testosterone reduction ≤0.5 ng/ml is more in degarelix treated group compared to control group (OR= 1.87, 95% CI: 0.89 to 3.96, p=0.1) after 28 days of ADT, but this difference is not statistically significant (Fig. 6). Heterogeneity did not account for a significant proportion of the variability between studies (I² = 0 percent).

PSA level reduction

Due to different measures for reporting PSA level reduction in different studies and high heterogeneity, there was no possibility to pool data and perform meta-analysis. In Axcrona’s (16) RCT, 82 patients received degarelix and 93 patients received goserelin (GnRH agonist) plus bicalutamide (anti androgen). The median percentage changes in PSA level were similar; for degarelix the decrease from baseline at weeks 4, 8 and 12 were− 80.6%, − 89.7% and − 92.0%, respectively whilst for goserelin they were − 85.2%,− 96.6% and − 97.3%.

In Anderson’s (18) experience, PSA levels were reduced by 90% at week 12 in both the degarelix (27 patients) and goserelin plus bicalutamide (13 patients) groups (mean reduction 92% versus 97%, respectively). Median PSA levels at this time point were less than 2 ng/ml in both groups. This result indicates that there is no significant difference between intervention and control groups.

In Mason’s (15) experience, like previously mentioned studies, there was no significant difference among degarelix treated (180 patients) and goserelin plus bicalutamide treated (64 patients) groups. The median percentage changes in PSA were also comparable; for degarelix the decrease from baseline at weeks 4, 8 and 12 were −71.6, −84.8 and −89.2%, respectively,
whereas for goserelin they were $-72.2$, $-93.1$ and $-93.0\%$.

In Klotz’s (13) study, 610 patients were randomized to 210 patients received degarelix240/80 mg, 206 patients received degarelix 240/160 mg and 204 patients received leuprolide (22 of them received concomitant anti-androgen). After 14 days, PSA levels had declined by 64%, 65% and 18% from baseline in the degarelix240/80 mg, degarelix 240/160 mg and leuprolide groups, respectively; after 28 days, the PSA declines were 85%, 83% and 68%, respectively. The differences in the reduction in PSA from baseline between degarelix and leuprolide patients at days 14 and 28 were statistically significant ($p<0.001$).

Safety outcomes

Drug induced mortality

Four studies (13,15,16,18) reported drug induced mortality. The comparison of the drug induced mortality between degarelix and GnRH agonist treated group is shown in Fig. 7. There was some heterogeneity that was not significant ($I^2=42\%$, $p = 0.18$).

Treatment-emergent adverse events (AEs)

Four studies (13,15,16,18) reported treatment-emergent adverse events. These four studies involved 875 patients, 479 receiving degarelix and 396 received GnRH agonists. Pooled data from these studies revealed that generally drug and treatment induced adverse events are similar among groups (OR=0.97, 95% CI: 0.2 to 2.96, $p=0.69$) (Fig. 8). Heterogeneity did not account for a significant proportion of the variability between studies ($I^2=0$ percent).

Hot flashes

We pooled data from four studies (13,15,16,18), (875 patients, 479 receiving degarelix and 396 received GnRH agonists) which reported hot flashes as an important treatment induced adverse event. Meta-

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig6.png}
\caption{Comparison of testosterone level reduction between degarelix and GnRH agonist treated group after 28 days.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig7.png}
\caption{Comparison of drug induced mortality between degarelix and GnRH agonist treated group.}
\end{figure}
analysis results revealed that degarelix and GnRH agonists are similar in this outcome (OR=1.04, 95% CI: 0.75 to 1.44, p= 0.83) (Fig. 9). Their heterogeneity was not important. (I²= 13%).

### Injection site reaction

Injection site reactions including pain, erythema, pruritus, swelling and induration; are the most prevalent and important adverse event. Four studies (13,15,16,18) reported injection site reactions. These four studies involved 875 patients, 479 receiving degarelix and 396 received GnRH agonists. Pooled data from these studies revealed that the degarelix S.C. injection was associated with a higher rate of injection site reactions than with the GnRH agonist injection (OR=46.34, 95% CI: 15.79 to 136, p≤0.001) (Fig. 10). Heterogeneity did not account for a significant proportion of the variability between studies (I²= 0 percent).

### Other adverse events

Besides above mentioned important treatment induced adverse events, there are some rare adverse events which reported in different studies. According to Klotz study (13), urinary tract infection (9% versus 3%, respectively; p< 0.01) and musculoskeletal...
and connective tissue AEs (26% versus 17%; p< 0.05) were more common with leuprolide. Other complications like cardiovascular and cerebrovascular accidents, weight gain and arthralgia were the same among different groups. In Axcrona study (16), erectile dysfunction (degarelix, 5%; goserelin, 4%) and hyperhidrosis (degarelix, 4%; goserelin, 5%) were reported besides other prevalent AEs, which were similar among groups. The Anderson study (18), also showed lower incidence of urinary tract infection in degarelix treated group.

Discussion
Hormone therapy using GnRH receptor agonists and recently antagonists is the main treatment for locally advanced and metastatic prostate cancer. There are many studies assessing and comparing ADT desired and adverse effects on patients (9, 19-24). We performed this study to compare safety and efficacy of degarelix, with Gonadotropin-releasing hormone (GnRH) agonists using best available evidence to provide further evidence for informed policy making about using degarelix instead of GnRH agonists.

This systematic review provides some evidence that, for patients with locally advanced and metastatic prostate cancer, the only statistically significant treatment effect in degarelix treated groups (compared with GnRH agonists group), which lasts beyond first month of treatment is improvement in LUTS. This is measured by International Prostate Symptom Score (IPSS) at week 12, (MD= -1.85, 95% CI: -2.97 to -0.72, p=0.001). However, the QOL of patients, which is measured as a single question in the IPSS questionnaire, was not different among groups.

In first 28 days of treatment the testosterone reduction \( \leq 0.5 \) ng/ml is significantly more in degarelix treated groups compared to control groups. (OR=11.58, 95% CI: 5.77 to 23.22, p<0.001) but after first month, this difference is not statistically significant anymore (OR= 1.87, 95% CI: 0.89 to 3.96, p=0.1). The PSA reduction like testosterone reduction is more in degarelix treated groups at days 14 and 28 of treatment. These important outcomes were the same in both GnRH agonists and antagonists after first month of treatment and also in the subgroup of GnRH agonists treated patients receiving concomitant anti androgen from the first days of treatment.

Most reported AEs were of mild to moderate intensity. Generally, the incidence of drug and treatment induced adverse events and the number of discontinuations due to AEs were similar among groups (OR=0.97, 95% CI: 0.7 to 1.33, p=0.84). The most frequently reported AEs in studies were flushing and injection-site reactions. Meta-analysis results revealed that degarelix and GnRH agonists are similar in hot flashes occurrence (OR=1.04, 95% CI: 0.75 to 1.44, p=0.83).

Additional analysis also showed that except for a more rapid onset with the GnRH antagonist, there were no major differences in the overall pattern of hot flushes between treatment options (12). Degarelix S.C. injection was associated with a higher rate of injection site reactions than with GnRH agonist injections (OR=46.34, 95% CI: 15.79 to 136, p\leq0.001).

Degarelix is generally well tolerated, without systemic allergic reactions. With the exception of injection site reactions, most AEs reflect androgen suppression or the underlying condition and are similar between degarelix and GnRH agonist groups (25). A pooled analysis of data from 1704 men in nine clinical trials showed that the rate of CVD events was similar before and after degarelix treatment in the overall patient population (26). Multivariate analysis showed that traditional CV risk factors of age, obesity and baseline CVD were associated with a higher CVD risk (p< 0.05). Degarelix dose and treatment duration were not independently associated with CVD events (26).

Limitations
Several problems exist in this review
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which needs to be addressed. Only 4 RCTs and 6 papers were suitable for inclusion in this study (11-13,15,16,18). While quality of studies were acceptable, but one RCT had been stopped recruiting patients early and so the sample size of that study was small (18). Considering the different mechanism of action between GnRH agonists and antagonists, measuring the outcomes in first days of treatment is important and some studies did not assess them. Also measurement of some outcomes like PSA level reduction was not the same in different studies and this prevented pooling data and performing Meta-analysis. Another issue was about receiving concomitant anti-androgen in GnRH agonist treated groups. Except for the Klotz study, the control group in other studies received anti-androgen. In Klotz study however just a small subgroup of the control group (22 from 202) received concomitant anti-androgen, it was not clearly mentioned that what has been the rational for selecting these patients. It is also to be mentioned that clinical trials included in this review were sponsored by Ferring Pharmaceuticals.

Conclusion

The different pharmacological profile of degarelix causes rapid testosterone and PSA suppression without the initial testosterone surge or microsurges associated with GnRH agonists. Degarelix efficacy in reducing testosterone and PSA level are not less than those of GnRh agonists (27-29). The point is that when we compare degarelix with GnRH plus anti-androgen, this rapid onset is not significant and the only difference is about more pronounced effects on lower urinary tract symptoms by degarelix (30). This difference despite similar effects on PSA and testosterone suppression, may suggest the mechanism on LUTS is independent of these markers (29-32).

When one compares different aspects of these drugs, the cost of treatment accounts as a key factor to make a cost effective decision for using degarelix instead of GnRh agonists in patients with metastatic and locally advanced prostate cancer. Performing an economic evaluation of degarelix will also provide further evidence for better decision making in our setting.

The authors state that there is no conflict of interest to declare.

Acknowledgment

This research has been supported by National Institute of Health Research of Iran grant number 91321/3241.

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Appendix 1

**MEDLINE search strategy**

1. (degarelix OR firmagon OR abarelix OR plenaxis).tw.
2. exp Gonadotropin-Releasing Hormone/
3. exp Hormone Antagonists/
4. 2 AND 3
5. ((luteinising OR luteinizing OR LHRH OR gonadotrop$ OR GNRH) AND (agonist$ OR antagonist$ OR blocker$)).tw.
6. (androgen deprivation OR ADT OR androgen suppression).tw.
7. Goserelin/
8. Leuprolide/
9. Triptorelin/Pamoate/
10. Buserelin/
11. (goserelin OR zoladex OR leuprORelin OR leuprolide OR triptorelin OR trelstar).tw.
12. (bicalutamide OR casodex OR bicalox).tw.
13. exp Androgen Antagonists/
14. 1 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13
15. 1 OR 5 OR 6 OR 11 OR 12
16. exp Prostatic Neoplasms/
17. ((prostate OR prostatic) AND (cancer OR carcinoma OR adenocarcinoma OR tumour OR tumor OR neoplasm$)).tw.
18. 16 OR 17
19. 14 AND 18
20. 15 AND 19
21. 19 not 20

**MEDLINE (adverse events search strategy)**

1. (degarelix OR firmagon),tw.
2. exp Gonadotropin-Releasing Hormone/
3. exp Hormone Antagonists/
4. 2 AND 3
5. ((luteinising OR luteinizing OR LHRH OR gonadotrop$ OR GNRH) AND (agonist OR antagonist OR blocker$)).tw.
6. (androgen deprivation OR ADT OR androgen suppression).tw.
7. Goserelin/
8. Leuprolide/
9. Triptorelin /
10. Buserelin/
11. (goserelin OR zoladex OR leuprorelin OR leuprolide OR triptorelin OR buserelin).tw.
12. (bicalutamide).tw.
13. exp Androgen Antagonists/
14. 1 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13
15. exp Prostatic Neoplasms/
16. ((prostate or prostatic) AND (cancer or carcinoma or adenocarcinoma or tumour or tumor or neoplasm$)).tw.
17. 15 or 16
18. 14 AND 17
19. (safe or safety or side-effect or tolerability or toxicity).ti,ab.
20. (adverse adj2 (effect or reaction$ or event or outcome)).tw.
21. 19 or 20
22. 14 AND 17 AND 21
23. 18 or 22