Clinics in Oncology

Research Article
Published: 22 Mar, 2019

A Randomised Controlled Trial to Determine the Effect of Triptorelin on Reduction of Prostate Volume Pre-Radiotherapy Compared with Standard Therapy (Goserelin)

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Abstract

Objectives: To evaluate the non-inferiority of cytoreductive efficacy and effect on QoL of neoadjuvant Triptorelin as compared with Goserelin.

Materials and Methods: Seventy-one patients with localised CaP were randomised to receive either neoadjuvant Triptorelin (n=37) or Goserelin (n=34). Prostate volume was measured (Transrectal Ultrasound (TRUS)), at baseline and 14 weeks after start of therapy. PSA, testosterone and QoL questionnaires were completed at baseline, 6, 10 and 14 weeks after start of therapy. Changes in TRUS volume, QoL scores; analysed as mean scores over the 4 treatment time points, were evaluated using analysis of covariance, with baseline as covariate.

Results: The mean (S.D.) reduction in prostate volume after 12 weeks of Goserelin and Triptorelin was 36.8% (18.3) and 30.7% (17.7), respectively (mean difference of prostate volume was 3.11 cc). Twenty-nine out of 34 in Goserelin group (85.0%) and 33/37 patients in Triptorelin group (89.0%) achieved castrate levels of testosterone. The median time-to-castration was 6.1 (95% CI: 5.8-6.5) and 6.4 (95% CI: 5.9-10.0) weeks for Goserelin and Triptorelin, respectively. There was no significant trend towards worsening QoL with either Goserelin or Triptorelin in the global (EQ5D), cancer-specific (QLQ-C30), and symptom scores in QLQ-PR25 questionnaire with the exception of hormone symptoms. The hormone symptoms showed an increasing trend over 4 treatment time points, with those in the Goserelin arm more affected (p=0.02) than patients in the Triptorelin arm, despite non-inferiority in cytoreductive effect.

Conclusion: To our knowledge this is the first reported prospective randomised data demonstrating the non-inferiority of Triptorelin in terms of cytoreductive efficacy and QoL scores in the neoadjuvant setting, as compared to Goserelin. Further validation, within a larger sample size is required to evaluate impact of hormone symptoms.

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Received Date: *28 Feb 2019*
Accepted Date: *20 Mar 2019*
Published Date: *22 Mar 2019*

Citation:
Bahl A, Challapalli A, Greenwood R, Kirk H, Garadi K, Bobruk K, et al. A Randomised Controlled Trial to Determine the Effect of Triptorelin on Reduction of Prostate Volume Pre-Radiotherapy Compared with Standard Therapy (Goserelin). Clin Oncol. 2019; 4: 1598.

Mini Abstract

This is a prospective randomised trial demonstrating the non-inferiority of Triptorelin in terms of cytoreductive efficacy and QoL scores in the neoadjuvant setting, as compared to Goserelin.

Keywords: Goserelin; Triptorelin; Cyto-reduction; Quality of Life; Neoadjuvant; Radiotherapy; Non-inferiority

Introduction

In UK, prostate cancer is the most commonly diagnosed malignancy affecting men beyond middle age, and is second only to lung cancer as a cause of cancer deaths [1]. Worldwide, there has been a consistent increase in the incidence of clinically significant disease in recent years [2,3].

External Beam Radiotherapy (EBRT) is used as a curative treatment in men with T1-T3 Prostate Cancer (PCa). Current practice guidelines advocate Neoadjuvant Androgen Deprivation Therapy (NADT) with radical radiotherapy especially when the PCa is intermediate-risk or high-risk [4,5]. The National Institute of Clinical Excellence (NICE) guidance (2014) recommends ADT for 3-6 months before receiving radical radiotherapy to the prostate; with those having a Gleason score ≥ 8 to continue the hormone therapy for a minimum of 2 years after radiotherapy treatment [5].

Luteinising Hormone Releasing Hormone analogues (LHRHa) work by mimicking the physiological actions of LHRH. Under normal physiological conditions, the hypothalamus stimulates the release of LHRH. This targets receptors on the anterior pituitary gland to stimulate both the synthesis and release of gonadotrophins; Luteinising Hormone (LH) and Follicle Stimulating Hormone (FSH). LH attaches to receptors on the Leydig cells of the testes promoting testosterone production, which is thought to play an essential role in prostate growth. It is thought therefore, that if testosterone levels are suppressed, prostate gland growth may also be impeded. The aim of NADT is to reduce the size of the prostate gland so that the area to be treated with radiotherapy is smaller, thus reducing the risk of damage to normal tissue near the prostate. It has been shown that three months of neo-adjuvant Goserelin reduces the prostate size to about 70% of its original volume thus reducing the linear dimensions of the prostate by about 10% [6]. Another study using Goserelin for 3 months showed a mean reduction in prostate volume of 26% when initial volumes were an average of 48.9 cm^3 [7]. Whilst this reduction may seem small (20% to 30%), it affects the extent of the rectum that is exposed to high dose radiation [8].

Most of the data on hormone therapies and interaction with radiotherapy relate to the use of Goserelin. Goserelin, when used for neo-adjuvant and/or adjuvant therapy has been shown to be beneficial in prostate cancer patients receiving radiotherapy with reduction in progression of the disease and improved survival [9]. Various LHRHa differ from each other in their relative potencies and plasma half-lives. Triptorelin is 100 times more potent that native LHRH. Adverse events associated with the use of ADT, such as hot flushes, erectile dysfunction, decreased libido, mood changes, metabolic syndrome and cardiovascular morbidity, have a deleterious impact on quality of life (QoL) [10]. However, there is paucity of data on the impact of QoL with NADT.

Therefore, we wish to test the hypothesis that Triptorelin should be as effective as Goserelin in reducing prostate volume prior to radical radiotherapy. This randomised controlled trial was designed to evaluate the non-inferiority in cytoreductive efficacy of Triptorelin as compared to Goserelin in the neoadjuvant setting. The effect of these on achieving castrate levels of testosterone and QoL will also be assessed.

Materials and Methods

Patients

Patients with histologically confirmed prostate cancer who are eligible for and have chosen radical EBRT, ECOG performance status ≤ 2, willing to comply with the trial interventions were included. This is a single-blinded, single-centre, randomised controlled trial where patients were randomly assigned(stratified block design) to Triptorelin 3 mg or Goserelin 3.6 mg administered every 4 weekly for 3 months under bicalutamide cover for 28 days. The Consort diagram is shown in Figure 1.

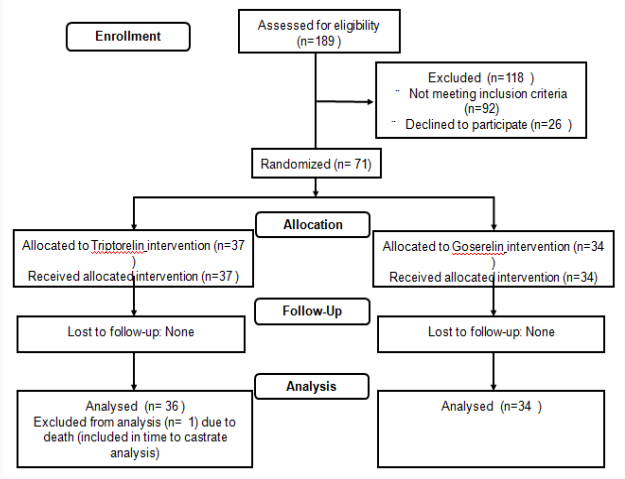

Figure 1: CONSORT diagram.

Assessments

The study schedule is as follows: Baseline (start of bicalutamide), 2 weeks (first LHRHa injection), 6, 10 and 14 weeks (visits 1-5, respectively). All patients had their prostate volume, width, length, and height measured using Transrectal Ultrasound (TRUS) conducted by the same radiologist (who was blinded), on the same ultrasound machine at various time points. The TRUS measurements were taken at baseline (up to 2 weeks before; prior to start of bicalutamide), and at visit 5 (14 weeks after start of Bicalutamide). The LHRHa injections were administered by the study team at visits 2, 3 and 4. Testosterone levels were assessed at visit 1, 3, 4 and 5. QoL questionnaires (EQ5D, QLQ-PR25 and QLQ-C30) were completed at all visits.

Treatment

All patients had subsequent radical EBRT and were followed up as per departmental protocol.

Statistical analysis

It was estimated that a sample size in each group of 32 patients, will have 80% power using a two group 5% two sided t-test, to detect a difference in mean total prostate volume of 10 cc or greater if the standard deviation is 14. If the mean prostate volume difference between Triptorelin and Goserelin will be <10 cc, then Triptorelin will be considered non-inferior to Goserelin. Allowing for up to 10% attrition, a total sample size of 71 patients were required. The data were analysed using intention-to-treat analysis. Descriptive statistics were used for quantitative measurements. Change in prostate volume, with baseline as covariate and without controlling for baseline were analysed using analysis of covariance (ANCOVA). Time to castrate levels of testosterone were taken to be the time from baseline to the first value <20 ng/dL. Kaplan-Meier curves were generated to estimate time to castration for Triptorelin versus Goserelin groups, which were compared using log-rank tests. Significance was accepted at $p<0.05$. The QoL scores were analysed as mean scores over the 4 treatment time points controlling for baseline using ANCOVA. Mean differences were reported with 95% confidence intervals and p values were given for the statistical significance. As there were 21 QoL scores analysed, the p value for statistical significance was considered to be the 0.25% level or a p value of less than 0.0025 (0.05/21 using Bonferroni correction).

Table 1: Patient Demographics.

Demographics	Triptorelin, n=37	Goserelin, n=34
Mean Age at screening (range)	71.8yr (57, 84)	70.9yr (62, 80)
Risk Stratification-n (%)	IR-8 (21.6%)	IR-9 (26.5%)
	HR-29 (78.4%)	HR-25 (73.5%)
Median PSA (ng/L) (IQR)	20.2 (11.6-39.6)	14.1 (8.2-24.9)
Median Testosterone (nmol/L) (IQR)	13.5 (10-20.2)	13.8 (11.5-17.5)
Median TRUS vol cc (IQR)	34.3 (27.3-46.2)	34.4 (29.4-45.2)

IR: Intermediate Risk; HR: High Risk; IQR: Interquartile Range

Results

Patients

A total of 71 patients were randomised into the study, 37 in the Triptorelin group and 34 in the Goserelin group. However one patient in the Triptorelin arm died and hence was omitted from the quality of life evaluations. Patient demographics were similar between the two groups as shown in Table 1.

Effect on Prostate volume

A comparison of baseline and follow-up data showed that the decrease in prostate volume was associated with baseline prostate volume (correlation coefficient: 0.54) whereas the percentage reduction was independent of baseline prostate volume (correlation coefficient: 0.0005). Prostate volume change was therefore analysed both as final volume controlling for baseline as described in the protocol, as well as percentage reduction (Table 2, Supplementary Figure 1).

Reduction in prostate volume was higher in those who had larger prostate volumes at baseline. The reduction in prostate volume was 30% in those on Triptorelin and 37% for those on Goserelin. This difference in volume was only 3 cc between the 2 groups and this was not found to be statistically significant, as this study was not powered to detect differences of less than 10 cc. Hence, the cytoreductive efficacy of Triptorelin is non-inferior to that of Goserelin.

Effect on serum testosterone

Castrate levels of testosterone were achieved in 85.3% (29/34) and 88.89% (32/36 patients) of patients treated with Goserelin and Triptorelin, respectively. The median time to achieving castration was6.1 (95% CI: 5.8-6.5) and 6.4 (95% CI: 5.9-10.0) weeks for Goserelin and Triptorelin, respectively (p=0.72, Log Rank test.

Effect on quality of life (QoL)

There was no clinically significant difference or trend towards worsening QoL with either Goserelin or Triptorelin in the global (EQ5D) and cancer-specific (QLQ-C30) domains. The cancer-specific (QLQ-C30) symptom score also showed no trend towards worsening QoL with either Goserelin or Triptorelin. Symptom scores in the QLQ-PR25 questionnaire did not show a significant difference between Goserelin or Triptorelin arms with the exception of hormone symptoms. The hormone symptoms showed an increasing trend over the 5 visits, with those in the Goserelin arm significantly (p=0.02) more affected (3 points higher on average) than patients in the Triptorelin arm, despite non-inferiority in cytoreductive effect and achieving castrate levels of testosterone (Table 3, Figure 2).

Discussion

We have shown that Goserelin and Triptorelin both caused a reduction in prostate volume and achieved castrate levels of testosterone. As the mean reduction of volume between the 2 groups was <10 cc, the cytoreductive efficacy of Triptorelin was non-inferior to that of Goserelin. Furthermore, there were no significant differences in QoL domains between Goserelin and Triptorelin, apart from hormones symptoms which were worse with Goserelin. To our knowledge this is the first reported prospective randomised data demonstrating the non-inferiority of cytoreductive effect and effect of Goserelin and Triptorelin, on QoL in the neoadjuvant setting in patients with PCa.

The hormone responsive nature of PCa was first demonstrated by Huggins and Hodges in 1941 [11], and lends itself to effective treatment with therapeutic agents that block the androgen receptor (Anti-Androgens (AA)) or agents that decrease the levels of testosterone (LHRH analogues and orchidectomy). Since then Androgen Deprivation Therapy (ADT) has been the standard of care for metastatic PCa [12].

For decades, the main stay of ADT was bilateral orchidectomy and estrogen administration. Despite orchidectomy being a reliable, inexpensive, and a very effective modality, it has been supplanted by medical castration, largely because of improved patient and physician acceptance [13]. In addition, both modalities are considered comparable [14], in spite of testosterone micro-surges on repeated injection [15] and lack of castrate levels as low as those achieved by bilateral orchidectomy in a minority of cases. Therefore, medical castration with LHRHa, and AA, have become the main form of ADT used [14]. LHRHa such as leuprorelin, goserelin, and triptorelin, are obtained by specific modification of the natural LHRH decapeptide, and differ from each other in their relative potencies and plasma half-lives. Triptorelin is 100 times more potent, structurally the closest and has a longer half-life than native LHRH and other commonly used LHRHa [16]. ADT aims to reduce testosterone levels to the levels achieved with surgical castration (defined as <50 ng/dl or <1.7 nmol/l, or more recently redefined as <20 ng/dl or <0.6 nmol/l, [17,18].

Whilst ADT has been the standard of care for metastatic PCa [12], its role in the neo-adjuvant setting has been the subject of 3 meta-analyses [9-21]. NADT prior to radical prostatectomy, although known to cause both clinical as well as pathological down-staging and a reduction in positive surgical margin rates, has not shown an improvement in Disease-Free (DFS) and Overall Survival (OS) [19].

Table 2: Change in prostate gland volume 12 weeks after first LHRH agonist injection.

Mean (S.D.) Prostate Volume (cc)	Triptorelin	Goserelin	Mean Difference between the two groups [95% CI]
Baseline	38.4 (16.7)	38.1 (12.8)	0.36 [-6.77, 7.48]
Follow up	26.9 (14.5)	23.8 (9.7)	3.11 [-2.82, 9.05]+
Reduction in volume	11.5 (7.1)	14.3 (9.5)	-2.87 [-6.20, 0.47]*
Percentage reduction	30.7% (17.7)	36.8% (18.3)	6.19% [-14.8, 2.41]

+The difference in follow-up prostate volume is estimated to be 3.11 with 95% confidence intervals which do not include 10 cc, confirming non-inferiority of Triptorelin.
*Controlling for baseline.

Table 3: Mean QoL scores for Goserelin and Triptorelin at 6, 10 and 14 weeks from baseline. Each domain scores range from 0 to 100.

Quality of life measure (n=34 patients in Goserelin group and 37 in Triptorelin group throughout except for sexual function and incontinence aids)	Mean treated score for Goserelin	Mean treated score for Triptorelin	Mean difference controlling for baseline	95% confidence interval for mean difference	p value
EQ5D - high is good					
	0.898	0.831	-0.027	[-0.082, 0.028]	0.332
EORTC C30 function scores - high is good					
Global health status	78.6	75.8	2.33	[-3.70, 8.37]	0.443
Physical functioning	92.7	88.6	-0.28	[-3.62, 2.06]	0.867
Role functioning	91.8	88.1	-1.09	[-5.48, 3.33]	0.627
Emotional functioning	91.7	88.1	1.23	[-3.23, 5.68]	0.584
Cognitive functioning	89.8	84.8	-3.73	[-8.98, 1.53]	0.162
Social functioning	94.4	90.3	-2.52	[-6.63, 1.59]	0.226
EORTC C30 symptom scores - high is bad					
Fatigue	18.8	21.5	-1.03	[-7.09, 5.04]	0.736
Nausea and vomiting	2.5	3.5	0.037	[-2.03, 2.10]	0.971
Pain	11	13.2	0.085	[-5.00, 5.12]	0.973
Dyspnoea	10	13.7	3.86	[-2.56, 10.29]	0.234
Insomnia	20.3	20.5	-0.67	[-9.07, 7.73]	0.874
Appetite loss	3.4	7	0.756	[-3.90, 5.41]	0.747
Constipation	9.8	8.3	0.554	[-4.38, 5.49]	0.824
Diarrhoea	3	3.8	0.346	[-3.13, 3.82]	0.843
Financial difficulties	2.9	5.9	-1.52	[-5.13, 2.10]	0.406
P25 symptom scores – high is bad					
Sexual activity (n=33,37)	23.1	17.1	-2.862	[-9.50, 3.78]	0.392
Sexual function (n=22, 19)	40.1	40.4	-4.93	[-14.4, 4.59]	0.299
Urinary symptoms (n=34, 37)	16.9	16.9	0.175	[-3.49, 3.84]	0.924
Bowel symptoms (n=34,37)	2.6	4.6	0.829	[-0.71, 2.37]	0.287
Hormone symptoms (n=34,37)	10.6	9	-3.319	[-6.10, -0.53]	0.02
Incontinence aid (n=4, 7)	3.6	4.2	+	+	+

+ Insufficient data for model to converge

NADT prior to radical radiotherapy causes reduction in prostate volume thus enabling optimal doses to be administered to the prostate, whilst reducing surrounding tissue exposure. Additional benefits include androgen suppression induced apoptosis and enhanced radio sensitivity due to reduced tumour hypoxia [22]. In contrast to the pre-prostatectomy setting, NADT pre-radiotherapy has been shown to reduce rates for local failure, progression to metastatic disease, and improve DFS [23], especially in patients with low Gleason scores. An improvement in biochemical DFS rates has also been reported in T2–T3 patients receiving NADT combined with radiotherapy [24]. The studies reviewed in the meta-analyses [23-27] have used Goserelin (Supplementary Table 1). Studies using Triptorelin [28,29] are listed in Supplementary Table 2. However, there is no formal direct comparison between the available agonists and all are considered to be equally active [13].

The biochemical effectiveness of ADT is measured by the proportion of patients achieving castrate levels of testosterone. Early trials of depot triptorelin were promising [30]. Various formulations of triptorelin have been shown to achieve and maintain castration 3-4 weeks after administration [31-37]: (Supplementary Table 3). In a phase III study of 120 men with locally advanced or metastatic PCa, 6-month formulation of triptorelin was shown to achieve castrate levels of testosterone in 97.5% of patient's after 28 days and in 98.3% after 12 months [37]. These results were replicated in the Tripto care study 1, 3, and 6 months after triptorelin injection in 326 adult men with locally advanced or metastatic PCa who were ADT naive [38], and with subcutaneous administration of triptorelin pamoate 3-month formulation [39]. In a comparative study with other LHRHa in patients with advanced PCa, Triptorelin and leuprolide demonstrated clinical equivalence in the proportion of men maintaining castrate serum testosterone levels, between 2 and 9 months after starting treatment [32]. However, Kuhn et al. compared the efficacy of triptorelin and leuprolide and showed that a significantly higher proportion of patients on Triptorelin had achieved castrate levels of testosterone 28 days after first hormone injection, although similar levels of PSA reduction in both groups was seen [36]. Our results compare favourably with these studies with 29 out of 34 in the Goserelin group and 33 out of 37 patients in the Triptorelin group achieving castrate levels of testosterone (<0.6 nmol/L), with no significant difference in the median time to achieving castration (6.1 (95% CI: 5.8-6.5) and 6.4 (95% CI: 5.9-10.0) weeks, respectively.

Prostate volume reduction is one of the advantages of NADT. An average reduction in volume by 24% to 55% of the initial volume

was observed after 3 months of NADT in various series [6,7,28,40-45] (Supplementary Table 4). For instance, Kuhn et al. demonstrated an overall significant reduction in prostate volume, with no significant reduction in prostate volume between the Triptorelin and leuprorelin group [36]. Similarly, our data has shown that the cytoreductive efficacy of neoadjuvant Triptorelin was non-inferior to that of Goserelin. The mean (± S.D) reduction in the prostate volume after 14 weeks of Goserelin and Triptorelin was 36.8 (± 18.4)% and 32.5 (± 20.9)%, respectively (difference of <10 cc with 95% CI not including 10 cc). Several studies have demonstrated a reduction in the volume of normal tissues that receive high doses of radiation after NADT due to a decrease in the prostate size, with statistically significant results [28,40,46]. The impact of the volume reduction on normal tissue doses in our dataset have not been presented here.

Adverse events associated with the use of ADT, such as hot flushes, erectile dysfunction, decreased libido, mood changes, metabolic syndrome and cardiovascular morbidity, have a deleterious impact on QoL [10]. In a prospective study comparing QoL outcomes in patients treated with surgery, external beam radiotherapy and brachytherapy, Sanda and colleagues have demonstrated a significant reduction in hormonal QoL outcomes in patients on ADT, which persisted for more than 2 years [47]. However, there are also reports of improvements in some aspects of health-related QoL (HRQoL) and satisfaction in patients [48-50]. In an observational study, 1438 prostate cancer patients initiating treatment with Triptorelin, 3- or 6-month formulations were evaluated for prescription and patient preference. The 6-month formulation (62.8% *vs.* 37.2% for the 3-monthformulation), was the preferred option due to simplification of the treatment regimen, fewer visits and patient satisfaction [50]. Another longitudinal, prospective study of elderly men aged ≥ 75 years has shown no adverse impact on HRQoL with 3-6 months of triptorelin treatment, with respect to urinary symptoms and incontinence [49].

However, there is paucity of data on the impact of QoL with NADT. We have evaluated the impact of 3 months of Triptorelin and Goserelin on QoL. We have shown that, there were no clinically significant differences in QoL (global (EQ5D) and cancer-specific (QLQ-C30)) domains, between Goserelin and Triptorelin, apart from hormone symptoms which were worse with Goserelin. Symptom scores in the QLQ-PR25 questionnaire did not show a significant difference between Goserelin or Triptorelin arms with the exception of hormone symptoms. The hormone symptoms showed an increasing trend over the 5 visits, with those in the Goserelin arm significantly (p=0.02) more affected (3 points higher on average) than patients in the Triptorelin arm, despite equivalence in cytoreductive effect and achieving castrate levels of testosterone. These findings are similar those of the TRIPTOSIX study, which showed generally stable global QoL (EORTC QLQ-C30 and QLQ-PR25 questionnaires) over 1 year [48].

In conclusion, Goserelin and Triptorelin both caused a reduction in prostate volume and achieved castrate levels of testosterone. The cytoreductive efficacy of neoadjuvant Triptorelin was non-inferior to that of Goserelin. There were no clinically significant differences in QoL domains between Goserelin and Triptorelin, apart from hormones symptoms which were worse with Goserelin. Further validation is required with effect on hormone symptoms as the primary outcome measure. To our knowledge this is the first reported prospective randomised data demonstrating the non-inferiority of cytoreductive effect and effect of Goserelin and Triptorelin, on QoL in the neoadjuvant setting.

Acknowledgement

The authors thank the investigators and patients who participated in this study. The study was funded by a grant from Ipsen and triptorelin used in this study was provided without charge by Ipsen.

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