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CLINICAL ARTICLE

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Effect of LHRH analogs on lower urinary tract symptoms associated with advanced prostate cancer in real clinical practice: ANALUTS study

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Abstract

Aims: To estimate the prevalence of lower urinary tract symptoms (LUTS) in patients with prostate cancer scheduled to receive LHRH analogs, and to assess the effectiveness of LHRH analogs on LUTS in patients presenting moderate/severe symptoms.

Methods: Prospective, noninterventional, multicenter study conducted at 28 centers in Spain and Portugal. LUTS were evaluated using the International Prostate Symptom Score (IPSS) at baseline, 24 and 48 weeks after initiation of treatment. Subanalyses were performed according to age and concomitant treatment (radiotherapy, alpha-blockers, and antiandrogens).

Results: A total of 354 patients were treated with LHRH analogs for 48 weeks. The percentage of patients with moderate/severe LUTS (IPSS > 7) decreased from 60.2% ($n = 213/354$) at baseline to 52.8% ($n = 187/354$) at Week 48. Among patients with moderate/severe LUTS at baseline: 73.7% ($n = 157/213$) still had moderate/severe

See Acknowledgment for the list of contributors.

LUTS at Week 48; percentage reductions of patients with LUTS at Week 48 were statistically significant ($p < 0.05$) overall and by age or concomitant treatment, except for alpha-blockers (84.2% patients receiving them still had moderate/severe LUTS at Week 48). All IPSS items, including quality of life for urinary symptoms, improved throughout the study. The only predictor of response to treatment with LHRH analogs that improved IPSS by 3 points after 48 weeks was baseline testosterone levels. Lower baseline testosterone levels were associated with greater improvement in IPSS after treatment with LHRH analogs (odds ratio 0.998, 95% confidence interval 0.996–1.000, $p = 0.0277$).

Conclusion: LHRH analogs have a positive effect in patients with locally advanced or metastatic prostate cancer presenting moderate/severe LUTS regardless of age or concomitant treatment received (radiotherapy, antiandrogens, or alpha-blockers).

KEYWORDS

androgen deprivation, concomitant, hormonal therapy, quality of life, radiotherapy

1 | INTRODUCTION

Lower urinary tract symptoms (LUTS) is a recent term for what used to be known as prostatism.[1] LUTS occur when men experience disturbances to their urinary flow, either in the form of storage symptoms (i.e., nocturia, frequency, and urgency) or voiding symptoms (i.e., hesitancy, intermittency, and weakened stream). Bearing these definitions in mind, the majority of literature on this subject refers to the LUTS complex generically as related to benign prostatic enlargement. However, it may also be present in patients with prostate cancer. In fact, 40% of the patients screened annually for prostate cancer showed moderate/severe urinary symptoms, and local prostate cancer treatment obviously affects LUTS.[2]

In comparison with age-matched controls, external beam radiotherapy (ERBT) may cause incontinence, stress incontinence and urinary pain, thus affecting quality of life (QoL); however, major long-term deterioration is not observed after 4 years of treatment.[3] Use of α1-adrenoreceptor antagonists is often considered in patients treated with radiation therapy, either prophylactically or at the earliest sign of LUTS deterioration.[4] Patients treated with brachytherapy have a much higher incidence of detrusor overactivity, prostatic and urethral strictures, and prostatic urethral stones, thus worsening LUTS.[5,6] Also, α1-adrenoreceptor antagonists tend to be used to improve LUTS in these patients.[7,8]

Androgen deprivation therapy (ADT) using LHRH analogs is a first-line treatment of symptomatic metastatic prostate cancer.[9,10] Also, different agents including LHRH agonists, LHRH antagonists, and antiandrogens are known to improve LUTS in these patients.[11–13] However, the prevalence of LUTS in patients with advanced prostate cancer is not well known and the effect of ADT on LUTS merits further investigation.

The intention of this study is to investigate the incidence of LUTS in patients with prostate cancer appointed to receive treatment with LHRH analogs, without a history of surgery or radiotherapy. In addition, the effect of LHRH analogs on the improvement of LUTS symptoms after 48 weeks of treatment is investigated.

2 | METHODS

2.1 | Study design

A prospective noninterventional study has been conducted at 28 centers in Spain and Portugal between July 2015 and September 2018 to investigate the prevalence of LUTS in patients with prostate cancer and the effect of LHRH analogs on the improvement of these symptoms over time.

The decision to receive LHRH analogs derived from routine clinical practice and was taken before enrollment in the study. Any LHRH analog was considered. Follow-up visits were also in line with current practice at each hospital. End of study visit was 48 ± 4 weeks after baseline visit.

Patients were screened for the presence of LUTS by the completion of the International Prostate Symptom Score (IPSS) that was evaluated at baseline, at 24 weeks, and at 48 weeks after the start of the treatment with LHRH analogs. All other procedures performed were in accordance with routine clinical practice. According to the standards of

radiotherapy available in participant institutions, differences in radiotherapy protocols that could have impacted the course of LUTS over time are not to be expected.

The study was approved by the ethics committees of participating centers.

2.2 | Participants

Inclusion criteria to participate in the study were adult patients who had been diagnosed with prostate cancer and were scheduled to receive an LHRH analog therapy; completion of IPSS questionnaire no more than 6 months before the initial visit and before starting LHRH analogs; and patients mentally fit for completing self-administered IPSS and written informed consent.

Exclusion criteria included any prostate surgery or pelvic radiotherapy performed before the study initiation; testosterone <50 ng/dL at first IPSS questionnaire; participation in any other clinical study within the last 2 months before study entry; and a life expectancy of less than 12 months. As this was a non-interventional study, no specific withdrawal criteria were specified.

To avoid bias in recruitment, investigators were not allowed to choose the patients but were asked to include all consecutive patients to achieve the recruitment target for the center during a period. However, if consecutive inclusions were not feasible, investigators have authorized to space the inclusions until achievement of the recruitment target.

Three populations were defined. The enrolled population was composed of all patients who signed informed consent form. The study population was patients with given informed consent and with total IPSS baseline data (V1) and without prior surgery or radiotherapy. Total IPSS baseline was defined as IPSS assessment prior, to the same date as or a maximum of 1 day after the first LHRH analog injection. The effectiveness population (EP) were patients from the study population that received LHRH analogs for 48 weeks and with total IPSS data at 24 weeks (V2) or 48 weeks (V3).

2.3 | Endpoint variables

The primary effectiveness endpoints included assessment of the number and percentage of patients with prostate cancer and LUTS at baseline (V1), and the percentage of patients suffering from prostate cancer with moderate/severe LUTS (IPSS > 7) at baseline (V1) and at 24 weeks (V2) and 48 weeks (V3).

Secondary endpoints included the assessment of the changes in the IPSS categories for each visit, the assessment of IPSS QoL due to urinary symptoms item at week 48, and the determination of predictive factors of response to LHRH analogs, considering as a response variable a reduction of total IPSS of at least 3 points.[14]

Demographics and baseline characteristics were recorded for the study population: age, tumor stage (TNM classification), time since first prostate cancer diagnosis, Gleason score, prior and concomitant treatments, PSA and testosterone levels, uroflowmetry, and prostate volume.

The IPSS consists of seven questions: four questions that deal with voiding symptoms (incomplete emptying, intermittency, weak stream, and straining to void) and three questions about storage symptoms (frequency, urgency, and nocturia). Each question is scored from 0 to 5 points. The total IPSS is calculated as the sum of the seven symptom question scores and ranges between 0 and 35. Four categories of total IPSS were defined: none or no symptoms (total score 0); mild symptoms (total score 1–7); moderate symptoms (total score 8–19); and severe symptoms (total score 20–35).[14] The eighth question of the IPSS questionnaire is relative to QoL due to urinary symptoms ("If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?"). This question is valued from 0 to 6.

No safety data were recorded in the clinical database and no statistical analyses of safety were planned in this study. Investigators were asked to report serious adverse events (regardless of causal relationship) and adverse drug reactions as in real-world clinical practice.

2.4 | Statistical analysis

Primary objectives were to estimate the prevalence of LUTS in patients with prostate cancer scheduled to receive LHRH analogs as part of prostate cancer management, and to assess the effectiveness of LHRH analogs on urinary symptoms in patients with prostate cancer presenting moderate/severe LUTS (IPSS > 7). Secondary objectives were to assess the QoL due to urinary symptoms and to investigate the predictive factors of response to LHRH analogs.

It was intended to enroll and collect data from 458 patients with prostate cancer requiring treatment with LHRH analogs. As this was an exploratory noninterventional observational study, the sample size was mainly based on feasibility. However, with this sample size, a two-sided 95% confidence interval (CI) for a single proportion using the exact method (Clopper–Pearson) would extend 4.72% from the observed proportion for an expected prevalence of 50%.

The prevalence of LUTS analysis was based on the study population. The number and percentage of patients having moderate/severe LUTS at baseline were presented using descriptive statistics including 95% CI for the percentage.

The primary effectiveness analysis was performed on the EP, firstly on overall patients and secondly on patients presenting moderate/severe LUTS at baseline. A subgroup analysis was performed according to age and concomitant treatment received. The number and percentage of patients with moderate/severe LUTS at week 48 were presented using descriptive statistics. To compare the proportion of patients with LUTS at Week 48 versus the proportion of patients with moderate/severe LUTS at baseline, paired McNemar exact test was used.

Secondary effectiveness analyses were performed on the EP and patients presenting moderate/severe LUTS at baseline. For each potential predictive factor, a null hypothesis that the regression coefficient for the factor is zero was tested using a logistic regression model. A threshold entry of 0.2 was considered for the stepwise multiple regression model. For quantitative factors, the odds ratio is presented for a one-unit increase.

All statistical tests were exploratory and two-sided at the 5% level of significance. The 95% CI of the proportions was calculated. Approximate binomial CI was produced using the Agresti-Coull method. Statistical evaluation was performed using the Statistical Analysis System (SAS)® (version 9.4).

3 | RESULTS

3.1 | Baseline patient characteristics

A total of 488 patients were screened in 25 sites in Spain and 3 sites in Portugal. Of them, 19 (3.9%) were not enrolled as they did not meet entry criteria. Of the 469 enrolled patients, 18 were excluded because protocol violation or other reasons. Thus, the study population was comprised of 451 patients (96.2% of enrolled patients) and an overall EP of 354 patients (75.5%) (Figure 1). Table 1 shows baseline patient characteristics for the study population.

3.2 | Prevalence of LUTS and effectiveness of LHRH analogs

The proportion of patients with moderate/severe LUTS (IPSS > 7) at baseline in the study population was 61% ($n = 275/451$), and in the overall EP was 60.2% ($n = 213/354$). According to age (>75 or ≤75 years) or concomitant treatment, the proportion of patients with moderate/severe LUTS at baseline was similar (Table 2).

The proportion of patients with moderate/severe LUTS in the overall EP decreased from 60.2% ($n = 213/354$) at baseline to 52.8% ($n = 187/354$) after 48 weeks of treatment with LHRH analogs (Figure 2A). This reduction was not statistically significant. In the different subgroups, the reduction was statistically significant only in patients of the overall EP without concomitant radiotherapy (63.5%–51.9%, $p = 0.0095$), without concomitant oral anti-androgens (63.1%–51.7%, $p = 0.0095$), and without alpha-blockers (57.6%–48.9%, $p = 0.0103$) (Table 2).

Considering only patients with moderate/severe LUTS at baseline, after 48 weeks of treatment with LHRH analogs 73.7% ($n = 157/213$) still had moderate/severe LUTS (Figure 2A). In this group of patients, the reduction was statistically significant ($p < 0.05$) whatever the age group or concomitant treatment received but with a lower decrease in patients receiving alpha-blockers (84.2% patients receiving them still had moderate/severe LUTS) (Table 2).

3.3 | Changes in IPSS and quality of life due to urinary symptoms

All IPSS items, including QoL due to urinary symptoms, improved throughout the study. In the overall EP, the mean total IPSS decreased from 11.03 ± 7.85 at baseline to 8.99 ± 6.60 at Week 48 ($p < 0.0001$).

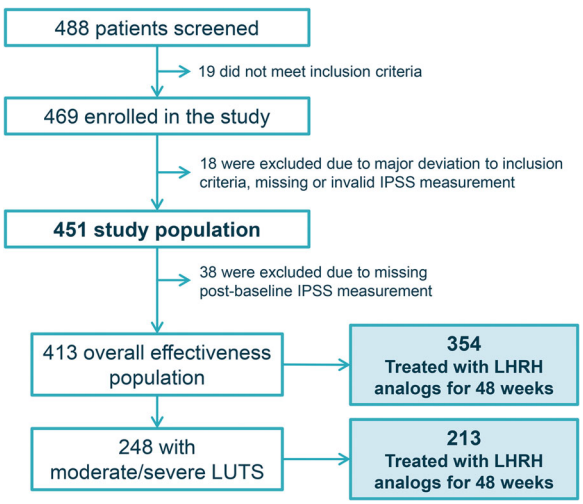

FIGURE 1 Patient disposition in the study. IPSS, International Prostate Symptom Score; LHRH, luteinizing hormone-releasing hormone; LUTS, lower urinary tract symptoms

TABLE 1 Baseline patient characteristics in the study population ($n = 451$)

Variable	N	%
Age, mean ± SD (years)	74.4 ± 7.1	
TNM ($n = 451$)		
T < 3, N0/NX, M0/MX	22	4.9
T ≥ 3, N0/NX, M0/MX	332	73.6
Any T, N1, M0/MX	32	7.1
Any T, any N, M1	65	14.4
Time since diagnosis, median (min; max) (months)	1.8 (0.0; 106.0)	
Gleason score, median (min; max)	7.0 (4.0; 10.0)	
Gleason score ($n = 451$)		
≤6	66	15.1
3 + 4	99	22.6
4 + 3	84	19.2
8	87	19.9
9–10	102	23.3
No data	13	
Previous treatments ($n = 451$)		
Oral antiandrogens	163	36.1
Alpha-blockers	44	9.8
5-α-reductase inhibitor	21	4.7
Concomitant treatments ($n = 451$)		
Oral antiandrogens	200	44.3
Radiotherapy	195	43.2
Alpha-blockers	73	16.2
Anticholinergics	8	1.8
Beta-3 agonist	5	1.1
PSA, mean ± SD (ng/ml) ($n = 439$)*	36.3 ± 82.6	
Testosterone, mean ± SD (ng/ml) ($n = 217$)*	414.6 ± 221.7	
Maximum flow, mean ± SD (ml/s) ($n = 101$)*	12.6 ± 7.3	
Post-void residual volume, mean ± SD (ml) ($n = 67$)*	31.6 ± 40.1	
Bladder volume, mean ± SD (ml) ($n = 89$)*	183.6 ± 101.7	
Prostate volume, mean ± SD (ml) ($n = 53$)*	43.0 ± 18.9	
Total IPSS, mean ± SD		
Overall effectiveness population ($n = 354$)	11.03 ± 7.85	
Effectiveness population with moderate/severe LUTS at baseline ($n = 213$)	15.77 ± 6.53	

Abbreviations: IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen; SD, standard deviation.

*Number of patients with available data for the parameter.

TABLE 2 Patients with lower urinary tract symptoms (LUTS) at baseline (V1) and week 48 (V3) visits

	Overall effectiveness population ($n = 354$)			Effectiveness population with moderate/severe LUTS at baseline ($n = 213$)		
Subgroups	**Baseline (V1) (%)**	**Week 48 (V3) (%)**	***p* Value**	**Baseline (V1) (%)**	**Week 48 (V3) (%)**	***p* Value**
All patients	60.2	52.8	0.0487	100	73.7	<0.0001
>75 years	65.3	57.7	0.0961	100	77.0	<0.0001
≤75 years	55.4	47.0	0.1325	100	69.2	<0.0001
With radiotherapy	56.6	52.4	0.5327	100	74.7	<0.0001
Without radiotherapy	63.5	51.9	0.0095	100	72.0	<0.0001
With oral anti-androgens	56.9	52.6	0.5327	100	72.9	<0.0001
Without oral anti-androgens	63.1	51.7	0.0095	100	73.6	<0.0001
With alpha-blockers	71.9	67.9	1.0000	100	84.2	0.0313
Without alpha-blockers	57.6	48.9	0.0103	100	70.6	<0.0001

p Value: Paired McNemar exact test.

In the EP with moderate/severe LUTS at baseline, mean total IPSS decreased from 15.77 ± 6.53 at baseline to 11.75 ± 6.39 at Week 48 ($p < 0.0001$). The reduction was statistically significant whatever the age group or concomitant treatment received. Both voiding (8.47 ± 4.61 to 5.73 ± 4.03) and storage (7.30 ± 3.21 to 6.04 ± 3.20) items decreased from baseline to Week 48. A reduction in IPSS score of ≥ 3 in this population was observed in 55.5% of the cases, and the proportion of patients with improvement in total IPSS score ≥ 25% baseline was 50.8%.

After 48 weeks of treatment with LHRH analogs, QoL due to urinary symptoms improved in both overall EP and patients with moderate/severe LUTS at baseline. Most patients are between categories 1–4 (delighted, pleased, mostly satisfied, and equally satisfied/dissatisfied with urinary symptoms) (Figure 2B).

According to IPSS categories, the percentage of patients with mild IPSS (score 1–7) increased slightly in the overall EP from baseline to Week 48 (37.6%–44.1%) and increased significantly in the population of patients with moderate/severe LUTS at baseline (0%–25.8%). Patients with moderate IPSS (score 8–19) did not change in the overall EP (44.6%–43.2%) and decreased in the group of patients with moderate/severe LUTS at baseline (74.2%–58.7%). Only patients with severe IPSS (score 20–35) decreased in both groups (15.5%–9.6% and 25.8%–15.0%, respectively) (Figure 2C,D).

Changes in prostate size were available in a small cohort in the EP ($n = 52$). Median (Q1–Q3) prostate volume changed from 42 (26–56) baseline to 28 (22–41) ml. There was no correlation between prostate volume change and IPSS change from baseline in these patients (Person coefficient 0.28; $p = 0.5$).

3.4 | Predictive factors of response to LHRH analogs

Because only one factor fulfilled the criteria for inclusion into the stepwise procedure, no stepwise multiple logistic regression modeling could be applied. The only predictor of response to treatment with LHRH analogs that improved IPSS by 3 points after 48 weeks was baseline testosterone levels. The level of testosterone at the start of treatment has an inverse relationship with the improvement in IPSS of more than 3 points that occurs at the end of treatment (Table 3). Age, PSA levels at baseline, Gleason score at baseline, time since diagnosis, or concomitant treatment were not considered predictors of treatment response.

4 | DISCUSSION

This non-interventional study was designed to characterize and investigate the frequency of LUTS in patients scheduled to receive LHRH analogs as part of prostate cancer management, and also to measure the overall effect of LHRH analogs in prostate cancer patients presenting moderate/severe LUTS (IPSS > 7).

The prevalence of LUTS in the overall population ranges from 4.8% for severe symptoms to 18.5% for moderate symptoms and increases with age.[15] In a previous report in Belgian patients with prostate cancer,

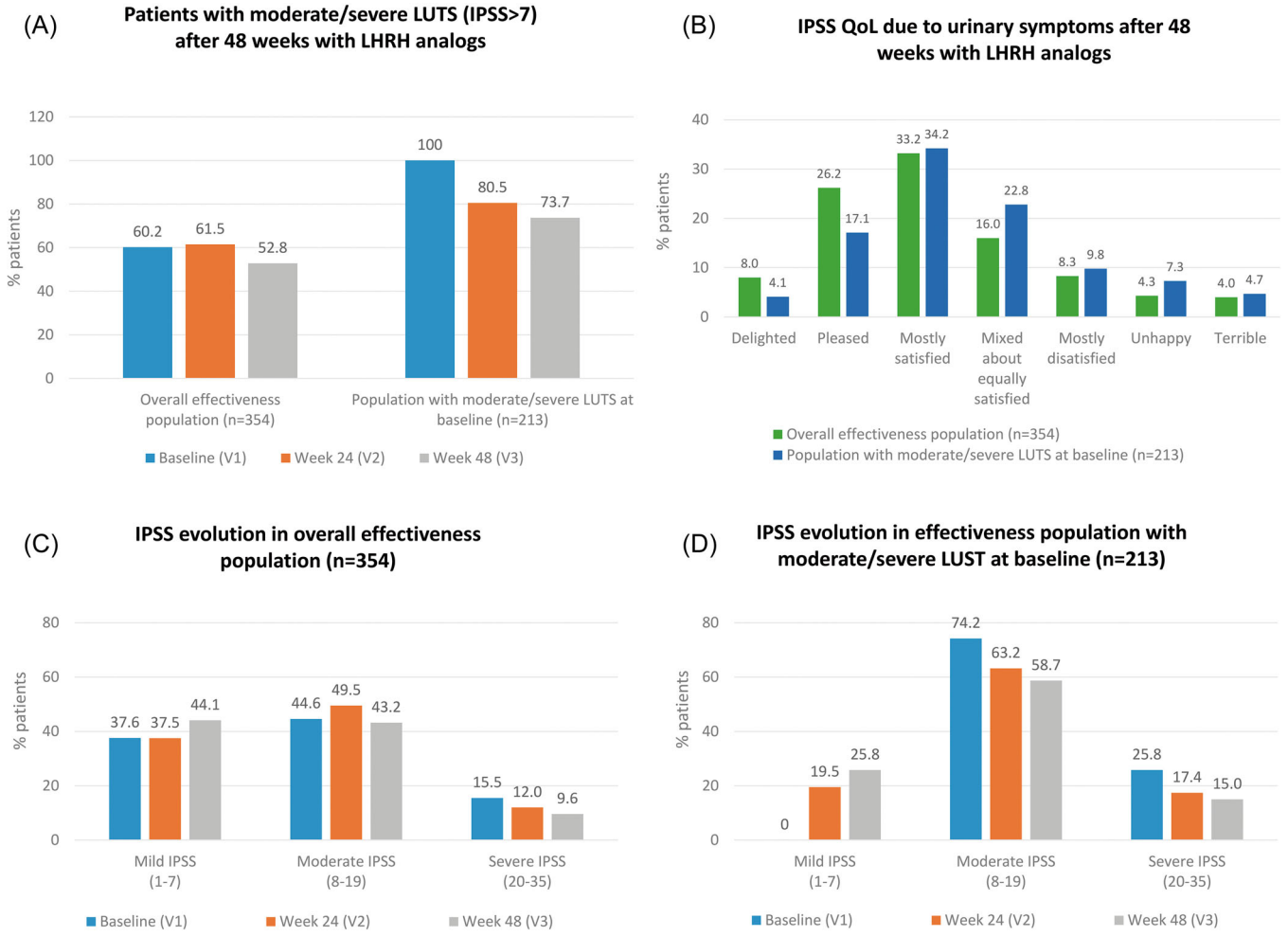

FIGURE 2 Changes in IPSS and QoL during the study: (A) Evolution of patients with moderate/severe LUTS (IPSS > 7) after 48 weeks of treatment with LHRH analogs in the overall effectiveness population ($n = 354$) and in the population of patients with moderate/severe LUTS at baseline ($n = 213$); (B) Distribution of IPSS QoL categories after 48 weeks of treatment with LHRH analogs in the overall effectiveness population ($n = 354$) and in the population with moderate/severe LUTS at baseline ($n = 213$). (C) Proportion of patients with mild, moderate, and severe LUTS during the study in overall effectiveness population ($n = 354$); (D) Proportion of patients with mild, moderate and severe LUTS during the study in the effectiveness population with moderate to severe LUTS at baseline ($n = 213$). IPSS, International Prostate Symptom Score; LHRH, luteinizing hormone-releasing hormone; LUTS, lower urinary tract symptoms; QoL, quality of life. **IPSS assessment at 48 weeks is at last available visit. For the vast majority of the patient (324/354) it is at 48 weeks but for the 30 remaining patients, it is at 24 weeks.*

61.5% had moderate/severe LUTS,[16] and in an observational grouped analysis of several countries, the prevalence of moderate/severe LUTS was 52.1%.[17] These results are similar to those in our study, with a prevalence of moderate/severe LUTS at baseline in the EP population of 60.2%. However, another study reported a prevalence of moderate/severe LUTS in Chinese patients of 93.2%.[18] These data highlight the differences in severity of LUTS between European and Chinese populations.

Several trials have assessed the impact of ADT on LUTS in patients with prostate cancer. A grouped analysis of several non-interventional studies initiated in clinical practice assessed the effectiveness of triptorelin in reducing moderate or severe LUTS in patients with prostate cancer. Following the administration of the drug, the proportion of patients with moderate/severe LUTS at baseline was reduced to 75.9% at Week 24 and to 67.2% at Week 48.[19] In other study, 31.3% of patients showed a clinically meaningful improvement in LUTS after 24 weeks of treatment with goserelin plus bicalutamide. Total IPSS showed a significant decrease from baseline at Weeks 12 and 24. While IPSS voiding score also decreased significantly from baseline to Weeks 12 and 24, IPSS storage score did not change significantly.[20] Although the effect of LHRH analogs observed in our study was somewhat smaller (80.5% and 73.7% of patients with moderate/severe LUTS

TABLE 3 Logistic regression analysis of the predictive factors of response to LHRH analogs in the effectiveness population with moderate/severe lower urinary tract symptoms at baseline

Univariate analysis*		
Factor	**Odds ratio (95% CI)**	***p* Value**
Age	0.996 (0.959–1.034)	0.8262
PSA at baseline (ng/ml)	1.000 (0.997–1.004)	0.9014
Gleason score at baseline	1.010 (0.777–1.313)	0.9409
Time since diagnosis (months)	0.994 (0.964–1.021)	0.6385
Concomitant radiotherapy versus no	0.742 (0.418–1.315)	0.3071
Concomitant alpha-blockers versus no	0.759 (0.371–1.551)	0.4471
Concomitant anti-androgens versus no	1.074 (0.604–1.911)	0.8085
Testosterone at baseline (ng/dL)	0.998 (0.996–1.000)	0.0277

Note: Response is defined as improvement in total IPSS ≥ 3.

Abbreviations: CI, confidence interval; IPSS, International Prostate Symptom Score; LHRH, luteinizing hormone-releasing hormone; PSA, prostate-specific antigen.

*97 observations were eliminated due to the absence of values.

at baseline still have these symptoms at 24 and 48 weeks, respectively), both IPSS voiding and storage scores decreased significantly. We could not demonstrate a symptomatic improvement caused by the decrease in prostate volume.

The reduction of LUTS observed in the overall EP was only significant in patients without concomitant treatment. This could be explained, at least in part, because the percentage of patients with LUTS at baseline was lower when they received concomitant treatment. The only exception was among those receiving alpha-blockers. The percentage of patients with LUTS at baseline who received concomitant alpha-blockers was higher than those who did not. Despite the fact that with the use of alpha-blockers there was a lower reduction of moderate/severe LUTS, according to the regression analysis, none of the concomitant treatments was a predictor of response to LHRH analogs (improvement of at least 3 points of the IPSS score). The worse outcome observed in patients who received concomitant alpha-blockers is possibly due to the fact that they had worse baseline characteristics. In any case, all patients experienced an improvement in LUTS as they all received LHRH analogs, regardless of age and concomitant treatment.

Our study also described an improvement in QoL due to urinary symptoms. Percentage of patients rating QoL as "mostly satisfied," "pleased," and "delighted" was 55.4% in the population with moderate/severe LUTS at 48 weeks. In another study that assessed the effect of triptorelin, this percentage was of 53.9% at Week 24 and 77.3% at Week 48.[21] However, the sample size of this study at Week 48 was smaller ($n = 22$) than in our study ($n = 213$). In addition, some patients in that study had previously received hormonal therapy and radiotherapy.

Another study described that only IPSS value was independently associated with a meaningful IPSS response.[20] In our study, the only predictor of response to treatment with LHRH analogs that improved IPSS by 3 points after 48 weeks was baseline testosterone levels. Lower baseline testosterone levels were associated with greater improvement in IPSS after treatment with LHRH analogs. We cannot explain how testosterone level before LHRH analogs administration predicts IPSS response in these patients. However, there is some related experience. A study performed on 50 Korean males revealed serum testosterone levels negatively correlate with IPSS and transitional prostate volume.[22] Another prospective study performed in Taiwan with 1752 middle-age men enrolled revealed high testosterone level is significantly associated with the presence of moderate/severe LUTS.[23] On the other hand, both human clinical trials and animal studies have shown that testosterone replacement therapy can improve LUTS, possibly by increasing bladder capacity and compliance and decreasing detrusor pressure at maximum flow rate (Q_{max}).[24,25] However, future studies are needed to better understand the relationship between testosterone level and male LUTS.

The main limitation of this study lies in the nature of its non-interventional observational design, so that no conclusions could be drawn according to the particular LHRH analog chosen. Also, it is not possible to draw appropriate conclusions according to the subgroups, since the number of patients in some of them is very small. Besides, discrimination between the positive influence of alpha-adrenergic blockers vs LHRH analogs on LUTS is another limitation. It should also be taken

into account that the same patient could have received more than one concomitant treatment.

5 | CONCLUSION

The prevalence of moderate/severe LUTS in patients with prostate cancer in the Iberian Peninsula is similar to that described in other studies. LHRH analogs have a positive effect in patients with locally advanced or metastatic prostate cancer presenting moderate/severe LUTS regardless of age or concomitant treatment received. In addition, the QoL due to urinary symptoms improved in these patients, suggesting a symptomatic relief upon treatment with LHRH analogs. Lower baseline testosterone levels were associated with greater improvement in IPSS after treatment with LHRH analogs.

AUTHOR CONTRIBUTIONS

Juan Morote: Data analysis and interpretation, critical revision of the article and final approval of the version to be published. **Antonio Gómez-Caamaño**: Data analysis and interpretation, critical revision of the article and final approval of the version to be published. **Javier C. Angulo**: Conception and design of the study, data collection, data analysis and interpretation, critical revision of the article and final approval of the version to be published. **Raúl Poza de Celis**: Data collection, critical revision of the article and final approval of the version to be published. **Francisco Gómez-Veiga**: Data collection, critical revision of the article and final approval of the version to be published. **Juan Pablo Ciria**: Data collection, critical revision of the article and final approval of the version to be published. **Jesús Calleja**: Data collection, critical revision of the article and final approval of the version to be published. **Javier Extramiana**: Data collection, critical revision of the article and final approval of the version to be published. **Maria Pérez-Sampietro**: Conception and design of the study, data analysis and interpretation, critical revision of the article, and final approval of the version to be published. **Valerie Perrot**: Conception and design of the study, data analysis and interpretation, critical revision of the article, and final approval of the version to be published.

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CONFLICT OF INTERESTS

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DATA AVAILABILITY STATEMENT

Where patient data can be anonymized, Ipsen will share all individual participant data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the study protocol and clinical study report, are not always available. Proposals should be submitted to DataSharing@Ipsen.com and will be assessed by a scientific review board. Data are available beginning 6 months and ending 5 years after publication; after this time, only raw data may be available.

ETHICS STATEMENT

This study has been approved by the Clinical Research Ethics Committee of all participating centers. The Ethics Committee of reference was that of Vall d'Hebron Hospital (Barcelona, Spain).

PATIENT CONSENT STATEMENT

Patients provided written informed consent form.

CLINICAL TRIAL REGISTRATION

Study number: A-ES-52014-219.

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