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Serenoa Repens, Lycopene and Selenium Versus Tamsulosin for the Treatment of LUTS/BPH. An Italian Multicenter Double-Blinded Randomized Study Between Single or Combination Therapy (PROCOMB Trial)

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BACKGROUND. Phytotherapy has been used to treat patients with lower urinary tract symptoms (LUTS). We evaluated the efficacy and tolerability of combination therapy between Serenoa Repens (SeR), Lycopene (Ly), and Selenium (Se) + tamsulosin versus single therapies.
METHODS. PROCOMB trial (ISRCTN78639965) was a randomized double-blinded, double-dummy multicenter study of 225 patients between 55 and 80 years old, PSA $\leq$ 4 ng/ml, IPSS $\geq$12, prostate volume $\leq$60 cc, Qmax $\leq$15 ml/sec, postvoid residual urine (PVR) $<$150 ml. Participants were randomized group A (SeR-Se-Ly), group B (tamsulosin 0.4 mg), group C (SeR-Se-Ly + tamsulosin 0.4 mg). The primary endpoints of the study were the reduction of IPSS, PVR, and increase of Qmax in group C versus monotherapy groups.
RESULTS. The decrease for combination therapy was significantly greater versus group A ($P < 0.05$) and group B ($P < 0.01$) for IPSS and versus group A ($P < 0.01$) for PVR from baseline

Conflict of interest: The authors declare no conflict of interest.

This study has been designed and conducted independently. Konpharma provided support for this study. Data collection and management and all statistical analyses were performed and retained by data manager (R.A.). The corresponding author and other co-authors interpreted the data and participated in the preparation, review and approval of the manuscript.

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to 6 months. A greater decrease in IPSS was observed for Group C versus group A ($P < 0.01$) and increase in Qmax versus group B ($P < 0.01$), from 6 months to 12 months. At one year, the changes of IPSS and Qmax were greater for Group C versus monotherapies (each comparison <0.05). The proportions of men with a decrease of at least three points (each comparison $P < 0.05$) and decrease of 25% for IPSS (each comparison $P < 0.01$) were greater for Group C.
CONCLUSION. SeR-Se-Ly + tamsulosin therapy is more effective than single therapies in improving IPSS and increasing Qmax in patients with LUTS. *Prostate 74:1471–1480, 2014.*

KEY WORDS: **serenoa repens; lycopene; selenium; tamsulosin; LUTS; BPH; phytotherapy**

INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most frequent causes of Lower Urinary Tract Symptoms (LUTS) in men and about 50% of men between 50 and 60 years suffer from this disease [1]. Even today, the exact molecular mechanisms underlying the development and progression of LUTS/BPH have not been fully understood. Certainly, recent studies have shown that chronic inflammation represents a crucial component in the pathogenesis of BPH, probably determining the hyperplasia of prostate cells. The inflammatory cells in fact, produce growth factors such as VEGF or TGF- β, which can support the fibromuscular growth in BPH [2].

In this context, medical therapy such alpha-blockers and 5-alpha reductase inhibitors or combination therapy have been used to relief symptoms and to prevent complications. The COMBAT and MTOPS studies have demonstrated the significant benefits of the combination therapy if compared with individual mono therapies [3,4]. However, despite the improvement in symptoms, side effects (erectile dysfunction, ejaculatory disorders, loss of libido) may limit adherence to treatment. For these reasons, some phytotherapics, like the lipid extract (LE) of Serenoa Repens (SeR) are currently used with the aim of improving symptoms and limiting the possible adverse effects.

SeR is frequently combined with other compounds like Selenium (Se) and the carotenoid lycopene (Ly) in the effort to increase its therapeutic activity in BPH.

Several mechanisms of action have been proposed to explain their therapeutic effects. The combined treatment with Se-Ly-SeR has been demonstrated to be more effective than SeR alone in preventing BPH and inhibited growth by 83%, suggesting that (Se) and (Ly) at pharmacological doses further increase *Serenoa repens* efficacy in BPH [5].

The LE of SeR would act by inhibiting the 5-alpha reductase and the binding between the diihydrotestosterone and the androgen receptor, antagonizing the α1- adrenergic receptor, and inhibiting cell proliferation and the production of COX-2 and 5-leukotrienes [6].

In addition, Ly and Se would act through some seleno-proteins promoting an optimal balance between oxidants/antioxidants, with significant beneficial effects on LUTS/BPH. Although these premises, several doubts still persist about the efficacy of phytotherapics in relief BPH/LUTS symptoms insomuch as the recent EAU and AUA guidelines did not recommended it [1,7].

Recent studies carried out on experimental models of bladder outlet obstruction, have highlighted how the combination between SeR, Se, and Ly is more effective than the single SeR in reducing prostate inflammation, the expression of growth factors, oxidative stress and prostatic hyperplasia [5,6].

On the basis of these observations, a combination therapy with alpha-blockers and SeR-Se-Ly certainly provides a rational pathophysiological, with the aim of ensuring a high therapeutic efficacy with limited side effects.

The following multicenter, randomized protocol, aimed to evaluate the efficacy and tolerability of the combination therapy between SeR-Se-Ly + tamsulosin versus the individual monotherapies with SeR-Se-Ly or tamsulosin in patients with LUTS/BPH.

MATERIAL AND METHODS

Study Design

From March 2011 to March 2012, 225 consecutive patients from 11 Italian centers were enrolled in this randomized, double-blinded, double-dummy multicenter study. The following trial was conducted in accordance with the ethical principles described in the Declaration of Helsinki and was approved by the local Ethical Committee. The present study, named as PROCOMB trial, is registered under number ISRCTN78639965.

Participants

The inclusion criteria were: age between 55 and 80 years old, digital rectal examination negative for prostate nodules, PSA ≤ 4 ng/ml, IPSS ≥ 12, prostate volume $\leq$60 cc (assessed by ultrasound), Qmax $\leq$15 ml/sec, postvoid residual urine $<$150 ml. Exclusion criteria were patients with prostate cancer, previous bladder cancer, diabetes mellitus, neurogenic disorders, severe liver disease, history of orthostatic hypotension or syncope, symptomatic urinary tract infection, anti-androgens, antidepressants (neuroleptics, anti cholinergics) therapy, recent treatment with an α blocker (within 1 month) or phytotherapy including saw palmetto extract (within 3 months), previous medical therapy with 5-ARI or surgical treatment for LUTS/BPH, patients with catheter or with an episode of acute retention of urine in the last 4 weeks.

After screening and possible pharmacological wash-out, the participants were off-site central randomized with a 1:1:1 ratio into three treatment arms each consisting of 75 patients.

Intervention

During double-blind treatment, patient received SeR-Se-Ly + placebo for one year (Group A), tamsulosin 0.4 mg + placebo for one year (Group B), or SeR-Se-Ly+ tamsulosin 0.4 mg for one year. Identical tablets were used to ensure that the blinded regimen was identical for all treatment groups.

Outcomes

The main outcome measures included IPSS, IPSS quality-of -life (QoL), IIEF-5, Qmax measured at uroflowmetry, post-void residual (PVR) and Ejaculation Questionnaire (EjQ), performed at enrollment (visit one), 1 month (visit two), at 3 months (visit three), at 6 months (visit four) and 12 months (visit five).

The Ejaculation questionnaire (EjQ) was based on the following scores: one = orgasm with a reduction in the strength of the semen, two = orgasm with a reduced amount of semen, three = orgasm without emission of semen, four = no orgasm.

The evaluation of the prostate volume by transrectal ultrasonography and Prostate Specific Antigen (PSA) tests were performed at visit one, visit four, and visit five.

The uroflowmetry was conducted with valid measurement of Qmax required a bladder filling measured $\geq$150 and $\leq$550 ml and a voided volume $\geq$125 ml.

Safety data were evaluated collecting adverse events (AEs). Treatment-related adverse events (TEAEs) were considered those reported for the first or worsened after randomization.

The primary endpoints of the study were the reduction of IPSS, increase of Qmax and the reduction of PVR in patients treated with combination therapy compared to single monotherapies after 1 year. We also evaluated the proportion of men with a decrease of at least three points and decrease of 25% for IPSS and with an increase of 30% of Qmax. Secondary endpoints of the study were considered the change in erectile function (assessed by the International Index of Erectile Function-5 questionnaire), prostate volume, serum PSA and QoL at 1 year.

One tablet of Profluss® consisted of 320 mg of supercritical CO_2 lipidic extract SeR containing 85% of fatty acids sterols, selenium (50 mcg) and lycopene (5 mg) (Ayanda AS, Norway) and distributed by Konpharma Srl (Rome, Italy).

Statistical Analysis

This randomized clinical trial was designed to enroll 75 patients for group (assuming a 10% drop-outs) using one-sided of a level of 0.05 with 90% power and assuming that the differences were assumed to be $>$2 with a standard deviation of four between the means of last IPSS of arm C versus B or A.

The patients enrolled were sufficient to evaluate the differences between arm C and B or arm C and A, in term of Q-max, using one-sided of a level of 0.05 with 90% power and assuming that differences were assumed to be $>$2 with a standard deviation of four.

The sample size was estimated based on the previous study [8]. The Mann-Whitney U Test was used for comparisons in the distribution of non-normal variables between a pair of treatment. The efficacy variables were tested as change from visit one to visit four, from four to five relative to primary endpoints and from baseline to visit five relative to primary and secondary endpoints. Qualitative outcome were tested using the Chi -Square Test ($\chi 2$ -Test) and z-test was used comparison of different between two proportion. A two sided P-value $<$0.05 was considered statistically significant in all the tests used. The rank analysis of covariance was used to evaluate the influence of difference value at the baseline.

RESULTS

Of all patients randomized, 219 have completed the 12 months of treatment (Fig. 1). Table I shows the baseline characteristics of the patients enrolled. Treatment groups were well balanced with regard to demographic and clinical characteristics at baseline. Of all subjects, median age was 65 years (range: 55–79),

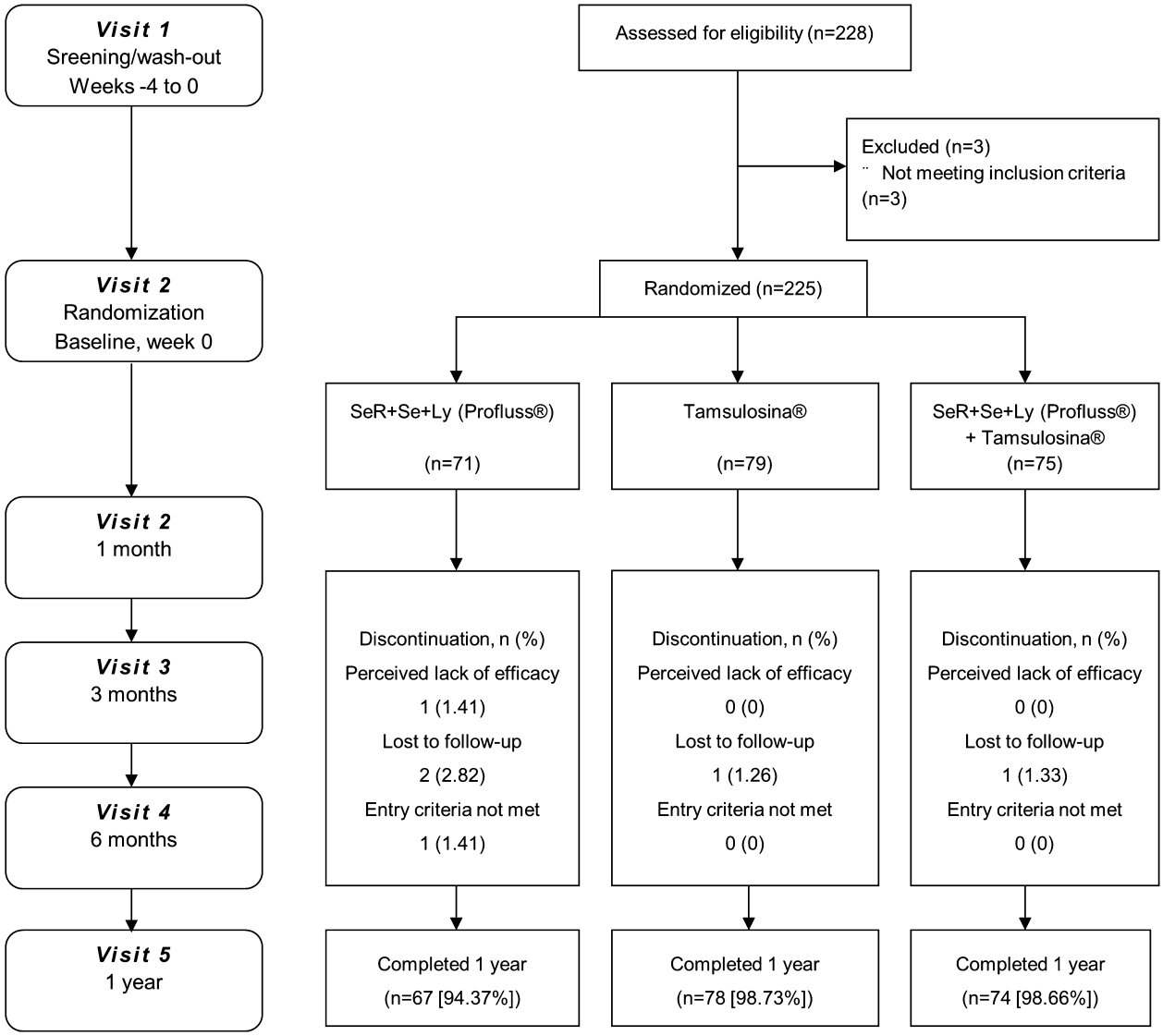

Fig. 1. Disposition of subjects. Subject Consolidated Standards of Reporting Trials (CONSORT) diagram.

TABLE I. Baseline Characteristics of the Patients.

	Group A Serenoa repens, lycopene and selenio (n = 67)	Group B Tamsulosin (n = 78)	Group C Serenoa repens, lycopene and selenio + tamsulosin (n = 74)
Age, median (range)	65 (55–79)	66 (56–79)	65 (56–76)
PSA (ng/ml/), median (range)	1.94 (0.15–4.0)	2.11 (0.14–4)	2.11 (0.38–3.87)
Prostate Volume (cc), median (range)	43 (17–60)	45 (20–60)	45 (20–60)
Qmax (ml/sec), median (range)	12 (5.4–15)	11.8 (4–15)	12.0 (6–15)
PVR (ml), median (range)	45 (0–130)	50 (0–140)	60 (0–140)
IPSS, median (range)	18 (12–35)	19 (12–33)	20 (12–35)
IIEF-5, median (range)	19 (1–25)	18 (1–25)	17 (1–25)
EjQ, median (range)	2 (1–3)	2 (0-3)	2 (0–3)
QoL, median (range)	3 (0–5)	4 (1–6)	3 (1–6)

median PSA was 2.1 ng/ml (range: 0.14–4), median Qmax was 11.8 (range: 4–15), median prostate volume was 43 cc (range: 17–60), median IPSS was 19 (range: 12–35), and median PVR was 50 cc (range: 0–140) (Table I).

Figure 1 shows the variation of primary end-points in the three groups of treatment. The decrease for combination therapy was significantly greater versus group A ($P < 0.05$) and group B ($P < 0.01$) in terms of IPSS and verses group A ($P < 0.01$) in terms of PVR from baseline to 6 months.

From 6 months to 12 months, Qmax significantly changed in Group C ($P < 0.01$) and PVR significantly changed in group B ($P < 0.01$). A significantly greater decrease in IPSS was observed for combination therapy versus group A ($P < 0.01$) and increase in Qmax versus group B ($P < 0.01$), from 6 months to 12 months. At 1 year, the median change of IPSS and of Qmax were significantly greater for combination therapy versus that of either monotherapy (each comparison <0.05). A significantly greater decrease in PVR was observed for combination therapy versus Group A ($P < 0.05$) at 12 months (Table II; Fig. 2).

The percentage change of IPSS was significantly greater for combination therapy versus tamsulosin (18.2% vs. 13.8%, $P < 0.05$) and versus SeR-Se-Ly (18.2% vs. 14.3%, $P < 0.05$).

TABLE II. Primary and Secondary End-Points Variations in Group A, B and C.

	Group A Serenoa repens, lycopene and selenio (n = 67)	Group B Tamsulosin (n = 78)	Group C Serenoa repens, lycopene and selenio + tamsulosin (n = 74)
IPSS			
Median (range) change from baseline	−3.0 (−13 to 3.0)	−3.0 (−20 to 8.0)	−4.0 (−17 to 5.0)
Median (range) change versus. group A	—	0 (−0.9 to 1.0)	−2.0 (−3 to −1)[§]
Median (range) change versus. group B	—	—	−2.0 (−3 to −1)[§]
Qmax, ml/sec			
Median (range) from baseline	2.0 (−5,3; 11)	2.0 (−8; 15)	2.3 (−3; 13)
Median (range) change versus. group A	—	0.1 (−1.0 to 0.8)	1 (0.001 to 2)[*]
Median (range) change versus. group B	—	—	0.8 (0.1 to 1.7)[*]
Post-void residue, ml			
Median (range) change from baseline	−10.0 (−70; 90)	−30.0 (−100; 80)	−34.5 (−112; 100)
Median (range) change versus. group A	—	18.0 (10.0 to 24.99)[§]	−20.0 (−30.0 to −10.0)[§]
Median (range) change versus. group B	—	—	−5.0 (−15.0 to 5)
IIEF-5			
Median (range) change from baseline	0.3 (−19.0 to 8.0)	0.2 (−5.0 to 4.0)	0.7 (−4.0 to 11.0)
Median (range) change versus. group A	—	0.0 (−1.0 to 1.0)	0 (−1.0 to 1.0)
Median (range) change versus. group B	—	—	1 (0 to 1.0)[§]
EjQ			
Median (range) change from baseline	−0.22 (−3.0 to 1.0)	−0.27 (−2.0 to 3.0)	−0.36 (−2.0 to 2.0)
Median (range) change from baseline	—	0.0 (−0.1 to 0.1)	0 (−0.1 to 0.1)
Median (range) change from baseline	—	—	0 (−0.1 to 0.1)
QoL			
Median (range) change from baseline	1 (−4; 3)	1 (−5; 2)	1 (−5; 3)
Median (range) change versus. group A	—	0.0 (−0.1 to 0.1)	0 (−0.1 to 1.0)
Median (range) change versus. group B	—	—	0 (−0.1 to 1.0)
PSA, ng/ml			
Median (range) change from baseline	0 (−1.40; 2.20)	−0.09 (−2.5; 3.13)	−0.16 (−1.74; 2.55)
Median (range) change versus. group A	—	0.1 (−0.8 to 0.3	−0.16 (−0.1 to 0.35)[‡]
Median (range) change versus. group B	—	—	−0.08 (−0.1 to 0.22)
Prostate Volume, cc			
Median (range) change from baseline	−1.5 (−14; 20)	−1.0 (−16; 12)	−2.5 (−15; 20)
Median (range) change versus. group A	—	0.0 (−1.0 to 2.0)	−1 (−0.1 to 2.9)
Median (range) change versus group B	—	—	−1 (−0.1 to 2.1)

IPSS = International Prostate Symptoms Score; IIEF-5 = International Index of Erectile Function; EjQ = Ejaculation Questionnaire; QoL = Quality of Life.

[*] $P < 0.05$.

[§] $P < 0.01$.

[‡] one-sided <0.05.

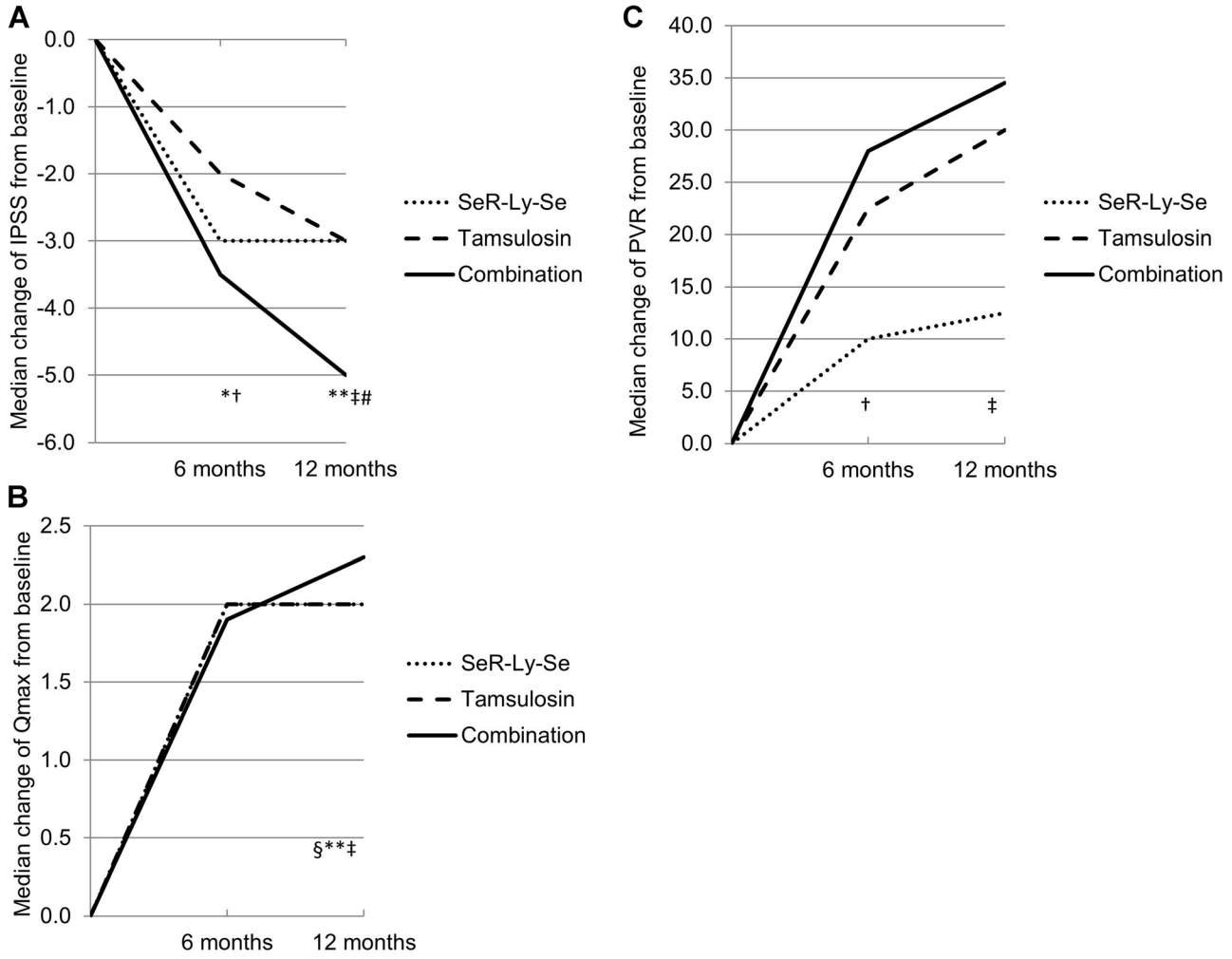

Fig. 2. Median differences of IPSS (A), Qmax (B), and PVR (C) from baseline to 6 and12 months in group A (SeR-Se-Ly), B (Tamsulosin), and C (Combination). *Indicates combination versus tamsulosin two-sided $P < 0.05$ at 6 months. †Indicates combination versus SeR-Se-Ly two-sided $P < 0.05$ at 6 months. §Indicates combination versus tamsulosin two-sided $P < 0.05$ from 6 to 12 months. #Indicates combination versus SeR-Se-Ly two-sided $P < 0.05$ from 6 to 12 months. **Indicates combination versus tamsulosin two-sided $P < 0.05$ at 12 months. ‡Indicates combination versus SeR-Se-Ly two-sided $P < 0.05$ at 12 months.

The percentage increase§ of Qmax for the Group C was greater versus Group A (24.0 vs. 15.4, $P < 0.05$) but not versus Group B (24.0 vs. 17.4, $P = 0.15$).

The proportions of men with a decrease of at least three points (each comparison $P < 0.05$) and decrease of 25% for IPSS (each comparison $P < 0.01$) were greater for combination therapy versus that of either monotherapy. The proportion of men with an increase of at least 3 ml/sec and of 30% of Qmax was not statistically different for combination therapy versus single monotherapies (Fig. 3).

Secondary Endpoints

In group C significant differences were demonstrated in terms of IIEF-5 between baseline and 12 months ($P = 0.032$). The QoL significantly varied in all treatment groups ($P < 0.001$). A significantly greater increase in IIEF-5 was observed for combination therapy versus group B ($P < 0.01$) and decrease of serum PSA ($P = 0.03$) at 12 months. No significant differences were observed in term of EjQ between groups.

There were no significant differences in terms of TEAEs between the groups ($P = 0.67$). One patient (1.4%) in group A drop-out for worsening of LUTS. No dropout occurred in group B and C because of any drug-related side effects. During the entire study, there was no evidence of significant variations with regard to laboratory parameters or vital signs.

Post-hoc Analysis

We performed a post-hoc analysis in patients suffering from erectile dysfunction (ED) at baseline (IIEF-5

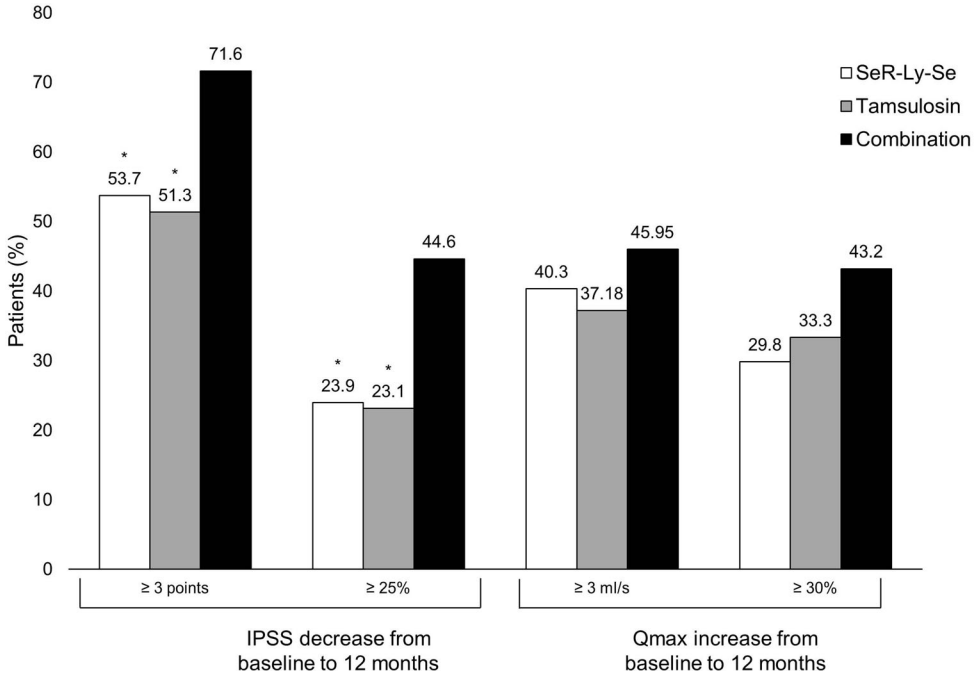

Fig. 3. Proportion of patients with improvement of IPSS and Qmax. *Indicates two-sided $P < 0.05$ versus combination. †Indicates two-sided $P < 0.01$ versus combination.

≤21). One hundred seventy (77.62%) patients had ED at the time of enrolment: 53 (79.10%) patients in group A, 58 (73.41%) in group B, 59 (78.66%) patients in group C. The median of the IIEF-5 was 17 (range1–21) in group A, 17 (range1–21) and 16 (range1–21) in group C. After 12 months of therapy, 16 (9.4%) of 170 patients do not exhibit ED: 8 (15.1%) in group A, two (3.4%) in group B, and six (10.2%) in group C. At the intergroup analysis between group A and group B, it was found a significant difference about the presence or the absence of ED post therapy ($P = 0.046$), while any difference between group A and C ($P = 0.57$) and between group B and C ($P = 0.27$).

DISCUSSION

SeR has been generally used for the improvement of symptoms in patients of LUTS/BPH. However, the scientific community still remain skeptics about its mechanisms of action or its therapeutic value. In this context, several clinical trials in the past have compared tamsulosin versus SeR therapy demonstrating a similar efficacy in reducing LUTS/BPH symptoms [9,10].

However, the recent European guidelines do not express a scientific opinion just because of the mentioned above bias [1]. Furthermore, a recent meta-analysis reported that SeR therapy does not improve LUTS or Qmax compared with placebo in men with clinical BPH, even at double and triple the usual dose [11].

Recent studies have proposed a triple combination between SeR and other essential trace elements like Selenium (SE) and the carotenoid lycopene (Ly) in the effort to increase its therapeutic activity in prostatic diseases. The rationale of this triple therapeutic approach could be the greater and the enhanced anti-inflammatory activity [6].

In this multicenter, randomized, double-blinded study, it has been evaluated for the first time the efficacy and the tolerability of the combination therapy with SeR-Se-Ly + tamsulosin 0.4 mg versus the individual monotherapies in patients with moderate-severe LUTS/BPH after 1 year of follow-up.

First of all we should noticed that after 6 months of treatment, combination therapy significantly improve symptom score compared with single therapy, while it was not demonstrated statistical superiority in term of Qmax. Interestingly, from 6 to 12 months, combination therapy demonstrated significant changes over tamsulosin group in term of Qmax.

In relation to the analysis of the primary endpoints, the combination therapy has been demonstrated to be more effective than the individual monotherapies in terms of reduction of the IPSS and of increase of Qmax after 1 year.

Indeed, the combination therapy resulted in a decrease of at least 3 points of the IPSS in 72% of cases,

in a reduction of 25% of the IPSS in 45% with significant advantages over each single therapy. Unfortunately, literature data on combination therapy are lacking.

In a retrospective study of 100 patients Argirovic of 2009, the addition of SeR to tamsulosin did not have any clinical benefit, such as a change in IPSS, Qmax or PVR[12].

A study published on 2009 by Hizli et al. evaluated the efficacy of combination therapy with SeR 320 mg + Tam or the individual monotherapies and no difference has been found between the treatment arms after 6 months of therapy in terms of IPSS and Qmax. However, even in this case no data are reported about the extraction of SeR, nor the power of the study [10]. Furthermore, the heterogeneity of the studies, the lack of long follow-up and of placebo and especially the diverse extraction of SeR still limit the correct interpretation about the effectiveness of SeR itself versus alpha-blocker [11].

It should be taken into account that the results from MTOPS and COMBAT studies showed considerable advantages of combination therapy with alpha-blockers and 5-ARI against individual monotherapies in patients suffering from LUTS/BPH [3,4].

In fact, the combination of these pharmacological classes allows the patient to benefit from each drug, potentially maximizing the therapeutic response. In addition, a sub -analysis of the study REDUCE (Reduction by Dutasteride of Prostate Cancer Events) has demonstrated the association between BPH and chronic prostate inflammation in 77% of cases in patients undergoing prostate biopsy. In addition, this study also demonstrated a statistically and clinically significant association between chronic prostatic inflammation and severity of LUTS, especially for the voiding symptoms [13–15].

In a further sub-analysis of the MTOPS study, Roehrborn et al. emphasized the role of chronic inflammation on the progression of BPH. In their study, inflammation was associated with a higher prostate volume and higher PSA values. Interestingly, patients with inflammation were at higher risk of experiencing an episode of AUR compared to those without inflammation (5.6% vs. 0% respectively, $P = 0.003$) [16].

To this regard, the anti-inflammatory effect on the prostate tissue potentially exhibited by LE of SeR was previously demonstrated by Navarrete et al. who reported a significant reduction in the levels of interleukin- 1 and TNF-α after 3 months of treatment with SeR compared to placebo [17]. More recently, Latil et al. have demonstrated that the LE of SeR inhibits the expression of two inflammatory mediators, the MCP-1/CCL2 and VCAM-1 [18]. Moreover, in a recent study on experimental models of bladder outlet obstruction, the combination of SeR-Se-Ly has proved to be more effective than the single SeR in reducing prostate inflammation, expression of growth factors, oxidative stress, and BPH. The inhibition of prostate growth induced by the SeR-Se-Ly is probably induced by increase of caspase-9, pro-apoptotic Bax, and reduction of anti-apoptotic Bcl- 2 [2,5,6,14]. Furthermore among the three compounds, Ly appears to give the major contribution in maximizing the effects of SeR-Se-Ly which induced activation of the programmed cell death [14].

All these mechanisms suggest that the addition of SeR-Se-Ly to tamsulosin may give rise to significant improvements of both LUTS symptoms and the urinary flow. This combination therapy may maximize the effects of each drug class, tamsulosin through the blockage of the α1- adrenergic receptor and the SeR-Se-Ly through anti-inflammatories and pro-apoptotics properties [19].

Finally, as reported in the literature, patients with BPH and chronic inflammation, not only have a higher risk of disease progression, but also lower rates of response to medical therapy [20,21].

Of course, the only accurate procedure to diagnose the presence of chronic inflammation of the prostate is the prostate biopsy. However it cannot be offered to all patients, but some less invasive remedies, such evaluation of severity of LUTS, serum PSA, and poor response to medical treatment, may help to identify patients with chronic prostate inflammation and risk of progression [22].

In this context, one may suppose to use combination therapy with SeR-Se-Ly and tamsulosin really in subjects with moderate LUTS/BPH and with chronic inflammation of the prostate, in order to optimize the benefits of both drugs.

Based on our results, the benefits of combination therapy appeared just after 6 months for symptoms and also of Qmax from 6 to 12 months.

In addition to these important considerations, several prospective studies have recently confirmed the close association between LUTS and ED [23], and the correlation between the severity of LUTS and the prevalence of ED [24]. About 77% of patients suffered from ED at the time of enrolment, confirming the strict relationship between LUTS and ED.

Interestingly, we found that combination therapy had significantly greater increase of IIEF-5 score compared to tamsulosin alone ($P = 0.01$). Our findings in terms of improvement of erectile function may be explained by the greater reduction in symptoms in the group treated with the combination therapy, and the possible reduction in the cellular infiltrate of inflammatory cytokines.

However, in the post-hoc analysis, only group A exhibit superiority over group B ($P = 0.046$). The lack of significance of combination therapy over tamsulosin alone, in term of absence of ED after therapy, may be explained by the greater LUTS improvement of these groups over group A. To this regards, we do not suggest to speculate about the possible efficacy of combination therapy in improving ED in patients with IIEF-5 $\leq$21.

Finally, it also should underline the lack of superiority of combination therapy versus each single therapy relative to the EjQ. This finding may be explained by the use of a not-validated characteristics of this questionnaire rather than the real differences between groups. Of course, our study is not avoided by some limitations. The small sample size should be taken into consideration. However, as shown by the determination of the power of the study, this sample size has guaranteed a study power of 90%, able to detect a reduction of at least two points of the IPSS and an increase of at least two points of Qmax. In fact, the lack of significance of proportion of men with increase of at least of 3 ml/sec and 30% of Qmax may be related to the small sample size. Finally the strengths of this study are the restrict criteria entry and that we demonstrated for the first time the greater efficacy of combination therapy with SeR-Se-Ly + tamsulosin in patients with LUTS/BPH after 1 year in term of improvement of symptom score and peak flow.

CONCLUSIONS

Combination therapy with SeR-Se-Ly + tamsulosin in for 1year was demonstrated to be more effective than the single monotherapies by improving IPSS and slightly Qmax in patients suffering from moderate-severe LUTS/BPH.

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