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Treatment of symptomatic benign prostatic hyperplasia with β-sitosterol: an 18-month follow-up

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Objectives To determine the long-term effects of phytotherapy with β-sitosterol (the trade name for β-sitosterol used in this study is Harzol®) for symptomatic benign prostatic hyperplasia (BPH).

Patient and methods At 18 months after enrolment in a 6-month multicentre double-blind placebo-controlled clinical trial with β-sitosterol (reported previously), patients were re-evaluated using the modified Boyarsky score, the International Prostate Symptom Score and quality-of-life index, the maximum urinary flow rate (Q_{max}) and postvoid residual urine volume (PVR). In this open extension of the original trial (after 6 months of treatment or placebo), patients were free to chose their further treatment for BPH.

Results In all, 117 patients (59%) were eligible for analysis during the follow-up. Of the former β-sitosterol group, 38 patients who continued β-sitosterol treatment had stable values for all outcome variables between the end of the double-blind study and after 18 months of follow-up. The 41 patients choosing no further therapy had slightly worse symptom scores and PVR, but no changes in Q_{max}. Of the former placebo group, 27 patients who started β-sitosterol after the double-blind trial improved to the same extent as the treated group for all outcome variables. The 18 patients choosing no further therapy showed no signs of improvement.

Conclusion The beneficial effects of β-sitosterol treatment recorded in the 6-month double-blind trial were maintained for 18 months. Further clinical trials should be conducted to confirm these results before concluding that phytotherapy with β-sitosterol is effective.

Keywords Benign prostatic hyperplasia, phytotherapy, β-sitosterol, long-term outcome, symptom score

Introduction

Phytotherapy has a long tradition in the medical treatment of BPH in Europe. Despite there being no established mechanism of action and no precise classification of the active compounds for many of these drugs, substantial symptom improvement has been reported in previous studies [1,2]. However, as modern drug therapies are becoming significantly more effective (e.g. α1-receptor blocking agents, 5α-reductase inhibitors), there is an obvious need for valid clinical testing of phytosterol drugs to confirm their claimed benefits.

Currently only two clinical trials have been reported that meet most of the study criteria of the WHO consensus conference for the treatment of BPH [3]. Both studies used β-sitosterol (the trade name for β-sitosterol used in this study is Harzol®) as the active treatment in their protocols [4,5]. The study design (multi-centred, placebo-controlled and double-blind) was similar in both trials and showed statistically significant improvements in BPH-related symptoms and urodynamic values during a 6-month study period.

Results for the 18-month follow-up of our previous trial [4] are now available for the primary (modified Boyarsky symptom score) and other outcome variables, e.g. IPSS, the quality-of-life (QoL) index, maximum urinary flow (Q_{max}) and postvoid residual urine volume (PVR) of the 200 patients originally recruited in the study group.

Patients and methods

After unblinding the 6-month randomized trial [4] both placebo and treated patients were free to choose further treatment or discontinue therapy of any kind. Inclusion criteria for the follow-up evaluation were designed to exclude possible false-positive effects and to maximize the number of patients eligible for evaluation. Therefore, all patients with a follow-up of $\geqslant 16$ months (486 days) after recruitment for the double-blind trial were included. To be eligible for analysis patients had to be continuously treated for at least 90% of the follow-up and no changes

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in treatment were allowed within the last 6 weeks before the follow-up visit. Patients were excluded from analysis if there was: loss to follow-up; surgical intervention for BPH; discontinuation of study medication during the double-blind trial; α1-blocker or finasteride therapy during the follow-up; any combination of β-sitosterol with other phytotherapy; and insufficient follow-up.

For the 18-month follow-up analysis, six groups resulted from the patients' choice of further therapy. Patients from the former β-sitosterol arm accounted for groups 1–3 according to their further treatment in the open extension and those in the former placebo arm accounted for groups 4–6 (Table 1).

During the follow-up patients were evaluated according to the original protocol of the double-blind trial. The magnitude of their symptoms was assessed using the modified Boyarsky score and the IPSS, and their Q_{max} and PVR were recorded.

Exclusion criteria applied in 83 patients (36 of the former β-sitosterol group and 47 from the former placebo group) of whom 32 had more than one reason for exclusion (Table 2). Eleven patients were excluded for BPH-related surgery, another seven because they discontinued study medication during the double-blind trial and seven because they were treated with α1-blockers or finasteride during the follow-up. Thirty-three patients were excluded from analysis as they were lost to follow-up. From the remaining 152 eligible patients, a further 25 were excluded because of insufficient follow-up. Table 2 also details the distribution between the original groups of patients excluded for each criterion.

The unpaired *t*-test was used to assess differences between all the variables in the original double-blind trial. The modified Boyarski score in the placebo-controlled study was originally evaluated in an intention-to-treat analysis. Other *P* values reported (compared with placebo) were considered descriptive only [4], as are all *P* values reported in the present analysis. The level of significance was defined as $\alpha = 0.05$ (two-sided).

Results

Of the 200 patients from the original protocol, 117 (59%) were eligible for the 18-month follow-up analysis; 41% were excluded for various criteria (Table 2). The treatment outcome for the primary and secondary variables is shown in Table 3. Those in group 1 continued to have a favourable outcome, with all values remaining stable from the end of the double-blind study to the 18-month follow-up. There was no additional effect from the longer treatment period. All improvements at 18 months were significantly better (except for PVR) than in those who never received active treatment (group 5).

Of the former placebo group, those in group 4 improved to the same extent as the treated group in the double-blind trial for all variables (Table 3). Symptoms and QoL improved more than in those who remained on watchful waiting (group 5), but the changes in Q_{max} and PVR were not significant because there were too few patients. Those in group 5 and those in group 6 (data not shown) had no or minor signs of improvement between the end of the double-blind study and at 18 months of follow-up.

Patients in group 2 showed mild worsening of symptoms and PVR (Table 3), but compared with the baseline values of the original trial, the improvement remained substantial. Comparing the 18-month follow-up values between group 2 and group 5, the changes in symptoms and QoL (IPSS) were significant. Patients in group 3 (data not shown) improved slightly compared with those who took no further medication.

Of the initial 200 patients, 15 (7.5%) reported undergoing surgery for BPH during the 18-month follow-up; 12 (6%) of these patients belonged to the former placebo group and three (1.5%) to the former β-sitosterol group. The mean time to surgery was 201 days in the patients on placebo and 441 in those taking β-sitosterol.

Discussion

To date, β-sitosterol has been tested in two randomized, placebo-controlled, double-blind clinical trials [4,5], and in many other trials of different design over the last two decades [6–8]. The first two trials were conducted following the WHO consensus criteria [3], except that

Table 1 The treatment groups in the open-extension trial

	Treatment during double-blind trial (n = *200*)	
Treatment in open extension trial (n = *117*)	*β-sitosterol* (n = *100*)	*Placebo* (n = *100*)
Group *N* (*n*)		
β-sitosterol	1 (38)	4 (27)
Watchful waiting	2 (14)	5 (18)
Other phytotherapy (data not shown)	3 (12)	6 (8)

Table 2 Reasons for exclusion from the 18-month follow-up evaluation. Note that exclusion criteria were applied in the order given, e.g. 15 patients had surgical interventions for BPH but four were already excluded as follow-up data were missing, thus the total number of excluded patients increased by only 11

	Excluded former:		*Additional event, however already excluded*		
Reason and order for exclusion	*Sitosterol*	*Placebo*	*Sitosterol*	*Placebo*	*Cumulative total*
Lost to follow-up	14	19	–	–	33
Surgical intervention	3	8	–	4	44
Medication discontinued during randomized trial	1	6	5	8	51
α-blocker or finasteride therapy	2	5	–	1	58
Combination phytotherapy	0	0	1	1	58
Follow up <486 days	16	9	4	8	83
Total	36	47	–	–	83

the study duration was 6 months in both. Both trials have shown β-sitosterol to be better than placebo over the study period for symptoms and uroflow variables. With the criticism that the study duration was insufficient to provide enough information about the long-term results, the present study was designed to investigate the outcome of the original study population of the β-sitosterol group one year after the end of the double-blind protocol [4].

From the 64 eligible patients taking β-sitosterol in the original study, only 19% chose to discontinue it after unblinding; most of the rest (59%) remained on β-sitosterol treatment. In these patients, the results were stable over the 18-month follow-up. Of the 53 eligible former placebo patients, most (66%) chose phytotherapy over watchful waiting (34%). Interestingly, when starting β-sitosterol therapy (group 4), the patients had the same extent of symptom relief as had those taking β-sitosterol during the randomized study. Despite the small groups, in general all those who chose sitosterol for further therapy (group 1 and 4) had significantly better symptom relief and QoL scores than those who remained on watchful waiting during the open extension (group 5). Of all eligible patients, most chose drug therapy after unblinding in both the β-sitosterol and placebo groups; overall, these patients had a substantial and lasting favourable effect compared with the symptom severity at randomization. Active treatment was generally better than watchful waiting.

To interpret the present results correctly, the sub-

Table 3 Results for the Boyarski score, IPSS, QoL, Q_{max} and PVR at various times during the study

	Mean (SD)				
Group/assessment	*Boyarsky score*	*IPSS*	*QoL*	*Qmax (mL/s)*	*PVR (mL)*
Group 1					
At randomization	14.9 (4.5)	13.7 (4.6)	3.0 (0.8)	10.5 (2.6)	62.2 (23.6)
After double-blind trial	6.9 (4.0)a,b*	6.8 (4.1)a,b	1.4 (0.8)a,b	17.8 (5.7)a,b	22.1 (29.5)b
At 18-month follow-up	7.1 (3.4)b	6.3 (3.1)b	1.4 (0.7)b	18.7 (5.9)b	23.3 (28.2)
Group 2					
At randomization	13.0 (3.2)	13.6 (2.7)	3.1 (0.9)	9.0 (2.8)	64.6 (15.3)
After double-blind trial	6.4 (3.8)d	5.8 (3.6)c,d	1.5 (0.9)	12.4 (5.4)	25.6 (18.7)d
At 18-month follow-up	7.4 (4.3)	7.0 (4.1)d	1.8 (1.1)d	12.5 (4.1)	48.0 (35.2)
Group 4					
At randomization	13.6 (3.5)	14.1 (4.2)	3.0 (0.9)	10.8 (3.3)	66.6 (30.6)
After double-blind trial	10.9 (4.2)	11.3 (4.7)	2.4 (1.0)	12.2 (5.9)	47.3 (27.1)
At 18-month follow-up	8.1 (3.9)e	7.7 (4.6)e	1.5 (0.9)e	14.8 (6.7)	32.5 (27.9)
Group 5					
At randomization	13.1 (2.9)	13.2 (3.1)	2.6 (0.9)	9.3 (2.3)	71.6 (23.8)
After double-blind trial	11.9 (3.8)	12.3 (3.4)	2.9 (1.0)	10.9 (3.8)	71.9 (28.5)
At 18-month follow-up	12.4 (4.9)e	11.7 (4.6)e	2.8 (1.2)e	10.4 (3.2)	70.7 (59.8)

$P < 0.01$ comparing changes from baseline at given time points between: a, group 1 and group 4; b, group 1 and group 5; c, group 2 group 4; d, group 2 and group 5; e, group 4 and group 5.

stantial group of 83 patients who were excluded from the follow-up evaluation (41.5% of the original recruited 200 patients) were analysed for possible effects on the results. Three major indicators of treatment failure, e.g. surgical intervention, choice of α1-blocker or finasteride therapy, and discontinuation of medication during the randomized trial, were more prevalent in those receiving placebo. In addition, more patients were lost to follow-up in the placebo than in the β-sitosterol group. Results from the randomized study phase for the excluded patients showed no substantial differences in outcome compared with those not excluded. Therefore, no relevant factors appeared to affect the results of the 18-month follow-up caused by the exclusion of these patients.

The proportion of patients undergoing BPH-related surgical intervention (7.5%) was about half that reported in the recent PLESS study with finasteride [9]. Of these 15 interventions, 12 were in patients receiving placebo and in those who chose no further therapy in the open extension, with only two in those treated with β-sitosterol. These findings further support the beneficial effect of β-sitosterol therapy. However, as the study was not designed to assess this criterion it remains unclear whether other factors than β-sitosterol were responsible for this effect. Thus, as with many medical therapies for BPH, it is unclear if surgery is postponed rather than prevented in the long-term.

In the open-extension protocol each patient was free to chose their further treatment. When the outcome values for patients after unblinding were compared with their choice of further treatment, no significant factors, e.g. treatment outcome or treatment arm, were predictive in any of the follow-up groups. Therefore, it appears that additional factors other than treatment outcome, e.g. personal or doctor's preferences, may have also been involved in the choice. Of 32 patients who apparently required no further therapy, 18 were in the former placebo group and of 22 patients who changed to other phytotherapy, eight were former placebo patients. This reflects the typical wide spectrum of BPH symptom bother and the relative indications for therapy. Thus, as with other medical treatment for BPH, frequent monitoring of symptoms during therapy is advisable and therapy should be interrupted if the symptoms are relieved.

Together with other phytotherapy agents, β-sitosterol is often criticised because the mechanism of action is unknown. As prostatic size remains mostly unchanged during treatment, a substantial endocrine mechanism of action is unlikely. However, as shown in a recent study from our group [10], β-sitosterol has a significant effect on stromal TGFβ production within the prostate *in vitro*. Whether the induction of TGFβ is responsible for symptom relief in patients with BPH remains unclear.

As there are no known major side-effects of β-sitosterol therapy and the effects are maintained over at least 18 months, β-sitosterol should be considered with other medical therapies for patients with symptomatic BPH; however, it remains unclear which type of patient with BPH would benefit the most from this therapy. In addition, further randomized clinical trials should confirm the present data, as the relatively few patients and brief duration of the double-blind study limit the conclusions drawn about the long-term results. As there are no pressure flow data, this therapy should be considered as symptomatic relief rather than removing obstruction. This should always be considered when symptomatic BPH is treated conservatively with β-sitosterol.

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