0022-5347/03/1704-1264/0
THE JOURNAL OF UROLOGY®

Vol. 170, 1264–1269, October 2003
Printed in U.S.A.
DOI: 10.1097/01.ju.0000084514.49252.64

A TRIAL STUDY: THE EFFECT OF LOW DOSE HUMAN CHORIONIC GONADOTROPIN ON THE SYMPTOMS OF BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT

Purpose: Human chorionic gonadotropin (HCG) is a glycoprotein hormone with multiple physiological functions. It interferes with mammary tumorigenesis and modulates growth and tumorigenesis in prostate cancer cells. In addition, HCG receptor transcripts and protein have been demonstrated in normal and hyperplastic prostate glands. Functionally HCG has a growth modulating effect on androgen independent prostate cell lines. We investigated the possible clinical effects of HCG on the symptoms associated with benign prostatic hyperplasia (BPH) in this trial study.

Materials and Methods: We performed a multicenter, double-blind, placebo controlled, randomized pilot study evaluating the effects of low dose HCG vs placebo in 101 men (50 to 79 years old) with BPH. The primary efficacy measure was the American Urological Association total symptom index score. Secondary efficacy parameters included peak urinary flow and sexual self-efficacy questionnaire changes.

Results: Low dose HCG appeared to positively effect moderate to severe BPH symptoms according to American Urological Association scores and sexual function but not peak urinary flow. No HCG induced changes were noted in prostate specific antigen or prostate volume.

Conclusions: These findings suggest that HCG may provide a well tolerated and beneficial therapy for BPH that will be investigated in subsequent studies.

KEY WORDS: prostate, prostatic hyperplasia, questionnaires, urodynamics, chorionic gonadotropin

Benign prostatic hyperplasia (BPH) is common in older men. Its symptoms can be progressive with urinary retention, bladder infection, bladder calculi and renal failure.[1,2] Although many men with mild to moderate symptoms do well without therapy (watchful waiting), others require aggressive medical therapy or surgical intervention. BPH has heterogeneous causes, including hormonal factors, growth factors and stromal-epithelial interactions as well as the effects of aging.[3] The disease pathology is also heterogeneous, as in biopsies in which the histological ratio of epithelium-to-smooth muscle varies substantially from 1:3 to 4:1.[3] Both α1-blockers, which regulate the obstructive dynamic aspects of BPH primarily by relaxing smooth muscle tone, and type II 5α-reductase inhibitors, which decrease the dihydrotesterone concentration that contributes to enlargement, have roles in medical management.[4]

Human chorionic gonadotropin (HCG) is a glycoprotein hormone endogenously secreted by the placenta that is composed of 2 noncovalently linked molecules, namely the α and the β subunits. The earliest indication of an association between HCG and neoplasms was the identification of HCG as a tumor marker.[5] Acevedo and Hartsock reported the expression of membrane associated HCG, its subunits and its fragments in 74 cultured human malignant cell lines.[6] A direct correlation was demonstrated between HCG and the 2 major characteristics of the cancer process, that is local invasion and metastasis. Other researchers detected and isolated a common receptor for luteinizing hormone and HCG not only in gonadal tissues, but also in male and female nongonadal tissues.[7]

The first published reports of a beneficial effect of HCG on cancer came when HCG was found to block tumorigenesis and metastasis of neoplastic Kaposi's sarcoma in immunodeficient mice.[8] Subcutaneous HCG and intralesional treatment of Kaposi lesions by HCG in patients with AIDS produced regression by apoptosis.[9,10] Studies of the modulating activity of HCG on growth and tumorigenesis in prostate cancer cells demonstrated a growth decrease, apoptosis and cell death in vitro in androgen dependent LNCaP cancer cells.[11] This cell line is known to express relatively high levels of HCG receptor protein.[12] The apoptotic affect of HCG was independent of androgen concentration and, in addition, HCG showed a growth modulating effect in androgen independent prostatic cell lines.[11] Furthermore, it has been shown that HCG has a direct antiproliferative effect on cultured breast epithelial cells.[13] The latter affect appears to be mediated by the glycoprotein hormone inhibin.[14]

Recalling that Tao et al reported luteinizing hormone/HCG receptor transcripts and receptor protein in normal and hyperplastic prostatic tissue,[12] we postulated that HCG at low concentrations may have clinical efficacy due to its effect on these tissues involved in BPH. We present the initial clinical

Accepted for publication May 9, 2003.
Supported by Milkhaus, Inc.
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† Financial interest and/or other relationship with Bristol Myers Squibb, Johnson and Johnson, Pfizer, Wyeth and Milkhaus.
‡ Financial interest and/or other relationship with Milkhaus Laboratory.

data demonstrating the safety and effectiveness of low dose HCG for the symptoms of BPH.

MATERIALS AND METHODS

We performed a multicenter, double-blind, placebo controlled, randomized clinical study. Community dwelling men 50 to 79 years old with moderate to severe lower urinary tract symptoms according to the American Urological Association (AUA) total symptom index[15] were recruited. We determined the safety and efficacy of low dose HCG for BPH symptoms.

Participants. Subjects were referred by their primary care provider or self-referred at sites approved by the institutional review board to perform this trial. After providing informed consent subjects underwent initial evaluation, including medical history, physical examination with digital rectal examination, electrocardiogram, chest x-ray, complete blood count, serum electrolytes, peak urinary flow (Qmax) determined by uroflowmetry using a Urodyn 1000 (Dantec Medical, Santa Clara, California), post-void residual urine volume (PVR) determined by ultrasound using a Bladder Scan (Diagnostic Ultrasound Corp., Redmond, Washington) and the Sexual Self-Efficacy Questionnaire (SSEQ).[16]

Subjects were included if these values were within normal ranges for age. All eligible subjects reported moderate or severe BPH symptoms, equivalent to a total AUA score of 8 or greater. Subjects should not have been on α1-blockers, type II 5α-reductase inhibitors or anticholinergic or sympathomimetic medications within 8 weeks of the initial evaluation. Exclusion criteria included a history of diabetes mellitus, uncontrolled hypertension or orthostatic hypotension, prostate cancer, prior prostatectomy, chronic prostatitis, bladder cancer, urinary tract infection, renal or hepatic insufficiency, an AUA total symptom index of 8, Qmax greater than 15 ml per second and residual bladder volume greater than 350 ml.

Interventions. This study consisted of 3 phases, including a 4-week placebo run-in period, a 12-week randomized treatment period and a 4-week followup. All subjects who passed the initial evaluation received a 4-week supply of placebo. Placebo consisted of bacteriostatic water administered as 1 drop under the tongue 4 times daily (1 after each meal and 1 before bedtime) for 28 days. Subjects were asked to record drug compliance, time of daily doses and any symptoms in a daily medication diary. They were also given a voiding diary to document daytime and nighttime voiding patterns.

At the end of the 28-day placebo run-in phase (week 4) physical examination was done and serum electrolytes, complete blood count, prostate specific antigen (PSA), Qmax and PVR were determined. Subjects also completed the AUA total symptom index and SSEQ. Those who showed a greater than 30% decrease in the AUA total symptom index score and an improvement of at least 3 ml per second in Qmax from the initial visit to the week 4 visit were considered placebo responders. They were excluded from the randomized treatment phase.

Randomization. Subjects who did not respond to placebo were randomized to receive 1 drop of HCG (0.5 United States Phamacopeia IU) or placebo under the tongue 4 times daily for 12 weeks. They were evaluated 1 week after being randomized (week 5), and again at weeks 8, 12 and 16. At each visit they underwent physical examination and measurement of serum electrolytes, total testosterone, complete blood count, PSA, Qmax and PVR, and completed the AUA total symptom index and SSEQ. All subjects were evaluated at a 4-week followup visit after completing the study. No study medications were administered during this period. Each subject was evaluated by the same procedures at week 20 that were used at the end of the randomization period (week 16) except prostate size was not determined.

HCG was administered in bacteriostatic water. Each dose (1 sublingual drop) of HCG solution contained 0.5 USP IU HCG. HCG solution had no color, no odor and no taste. Bacteriostatic water was used as the placebo agent. At each of the 3 participating sites a research pharmacist used a randomization list to prepare HCG and placebo solutions in 10 ml multiple use bottles with droppers. Investigators and subjects were blinded to the preparation that each subject received. Prostate volume was measured by digital examination by the same site investigator at baseline and again at week 16.

Outcomes. Efficacy assessment was accomplished at the beginning (baseline) and the end of the placebo run-in phase, at weeks 5, 8, 12 and 16, and at the 4-week followup visit (week 20). The primary efficacy measure was the AUA total symptom index score. Secondary efficacy parameters included AUA symptom index individual question scores, and subscores for obstructive and irritative symptoms, SSEQ, Qmax, prostate volume, PVR and PSA.[17]

The AUA total symptom index consists of 7 questions, including 3 on obstructive symptoms (intermittency, force and straining) and 4 on irritative symptoms (incomplete voiding, frequency, urgency and nocturia). Each question is scored from 0—not at all to 5—almost always. Thus, the total score is 0 to 35. Based on this total score BPH symptoms are rated as mild—0 to 7, moderate—8 to 19 and severe—20 to 35.

SSEQ is a validated sexual activity instrument consisting of 25 questions that are answered as "can do" or "can't do." The questions cover a range of sexual activities, including the ability to achieve and maintain erection adequate for intercourse. Specifically it evaluates the beliefs of a man about his sexual and erectile competence in various sexual situations and may be completed by the patient (to obtain self-ratings) or by his partner (to obtain corroboration). Higher scores indicate greater confidence in sexual competence. Respon-

TABLE 1. *Subjects excluded prior to randomization*

Reason	No. (%)
Placebo responder	8 (11.4)
Qmax 15 ml/sec or greater	30 (42.8)
PSA greater than 4 ng/ml	10 (14.3)
Insufficient voiding	4 (5.7)
Elected to stop	5 (7.1)
Total AUA score less than 8	3 (4.3)
Confirmed prostate nodules	2 (2.8)
Other	8 (11.4)
Total	70 (100)

TABLE 2. *Select adverse events in men with BPH according to treatment group*

Adverse Event	No. Placebo (%)	No. HCG (%)	p Value (Fisher's exact test)
Overall	53	48	
Rhinitis	7 (13.2)	6 (12.5)	1.00
Decreased libido	1 (1.8)	3 (6.3)	0.3439
Hypercholesterolemia	1 (1.8)	3 (6.3)	0.3439
Abdominal pain	1 (1.8)	3 (6.3)	0.3439
Low back pain	3 (5.6)	3 (6.3)	1.00
Headache	6 (11.3)	2 (4.2)	0.2740
Anemia	0	2 (4.2)	0.2234
Bronchitis	0	2 (4.2)	0.2234
Erectile dysfunction	0	1 (2.1)	0.4752
Asthenia	0	1 (2.1)	0.4752

TABLE 3. *Baseline evaluation*

	HCG	Placebo	p Value
No. subjects	53	48	
Mean AUA score ± SD	16.04 ± 4.96	15.87 ± 5.63	0.6094 (t test)
Mean Qmax ± SD (ml/sec)	11.19 ± 2.34	10.54 ± 1.98	0.1404 (t test)
Mean age ± SD	63.47 ± 6.44	66.41 ± 5.91	0.0190 (t test)
Mean sexual functioning ± SD (40 subjects)	81.32 ± 20.32	79.26 ± 10.03	0.4480 (exact Wilcoxon test)

TABLE 4. *Change from baseline to week 16 in AUA Score, Qmax and sexual functioning*

Treatment Group	No. Subjects	Mean Change ± SD (IQR)	p Value	
			Without Age	Age Adjusted
AUA score:				
HCG	48	−5.67 ± 5.27 (7.33)	0.0261 (ANOVA)	0.0238 (ANCOVA)
Placebo	53	−3.38 ± 4.88 (6.33)		
Qmax:				
HCG	47	0.34 ± 3.53 (3.97)	0.1340 (ANOVA)	0.1377 (ANCOVA)
Placebo	53	0.72 ± 15.39 (4.17)		
Sexual functioning:				
HCG	34	5.57 ± 11.96 (10.67)	0.0481 (exact Wilcoxon test with stratification, baseline sexual functioning)	0.0358 (exact Wilcoxon test with stratification, baseline sexual functioning × age)
Placebo	36	0.72 ± 15.39 (12.00)		

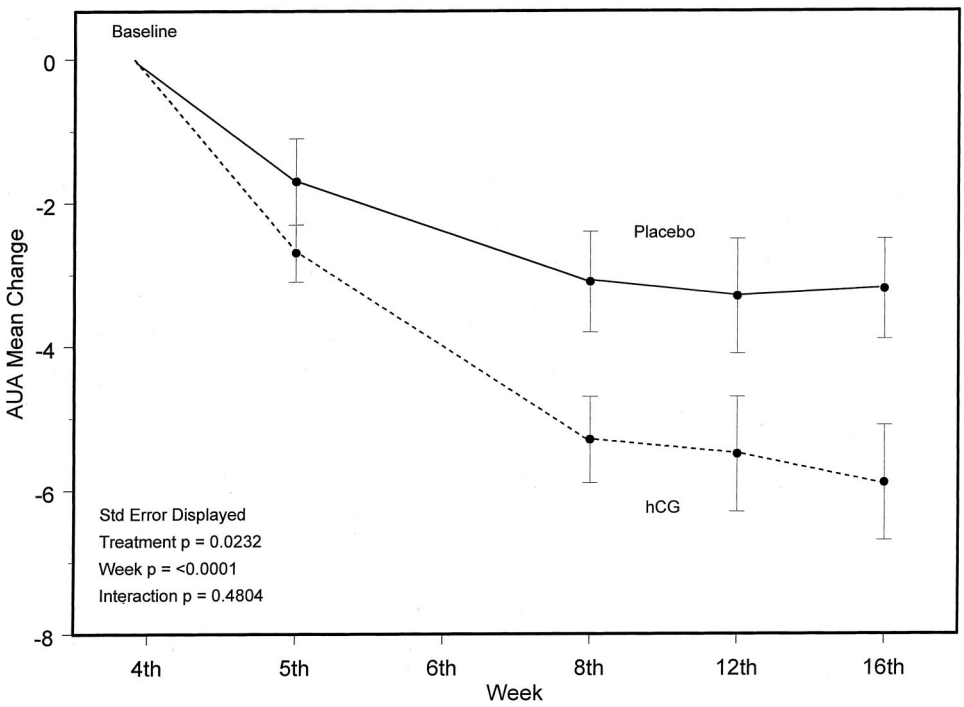

FIG. 1. AUA change from baseline for all weeks (baseline 8 or greater)

dents first indicate which sexual activities they expect they can complete and for each they rate their confidence level on 10-point interval scales of 10 to 100. The self-efficacy strength score is obtained by summing the values in the confidence column and dividing by 25 (the number of activities rated).

Statistical methods. Statistical analysis was performed on key baseline variables, the primary efficacy variable (AUA) and 2 important secondary variables (Qmax and SSEQ). Baseline AUA and Qmax scores, defined as the average of 3 pretreatment measurements (screening, pre-run-in and pretreatment), as well as subject age were evaluated using Student's t test. Racial composition was compared across treatments using Fisher's exact test. Due to extreme deviation from normality the averages of 3 pretreatment baseline sexual functioning scores were evaluated across treatments using the exact Wilcoxon test. In addition, the distribution of average baseline sexual functioning scores was stratified into quadrants and the relative frequency of patients across strata was then compared between treatments by Fisher's exact test. Stratification was done in light of the fact that subjects near either extreme of the sexual functioning scale were subject to a ceiling or basement effect, which disallowed a bidirectional response following treatment.

Week 16 changes from baseline in AUA and Qmax were evaluated using ANOVA with and without covariate adjustment for age. The 2 change scores met the underlying assumptions of normality and homogeneity of variance. Change in sexual functioning from baseline to week 16 showed a distribution with flat tails and a dense central region, as would be expected given the constraints noted for subjects at the extreme ends of the scale. Therefore, change scores for sexual functioning were analyzed using the exact stratified Wilcoxon test with the strata reflecting the baseline sexual functioning quadrant of a subject fell, or the baseline quadrant and dichotomization level of subject age according to the median age of 63 years (63 years or less vs greater than 63). Briefly, significance levels were derived for each efficacy variable using statistical techniques that were void of assumption violations. Furthermore, each analysis was done with and without adjustment for baseline age.

RESULTS

Recruitment and baseline data. Of the subjects screened for study eligibility 171 were entered into the placebo run-in phase. After 28 days of placebo treatment 101 subjects were eligible for the randomization phase of this study. Table 1 lists the reasons for exclusion for the 70 subjects not eligible to continue in the study. The majority of screening failures were due to unacceptable urodynamic (Qmax) results (43%)

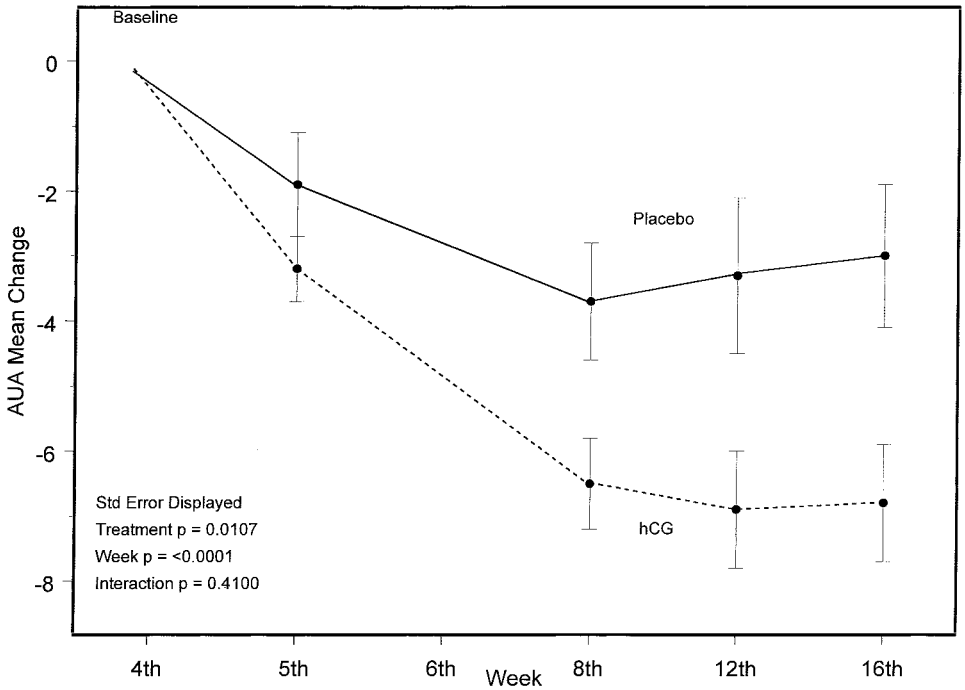

FIG. 2. AUA change from baseline for all weeks (baseline 13 or greater)

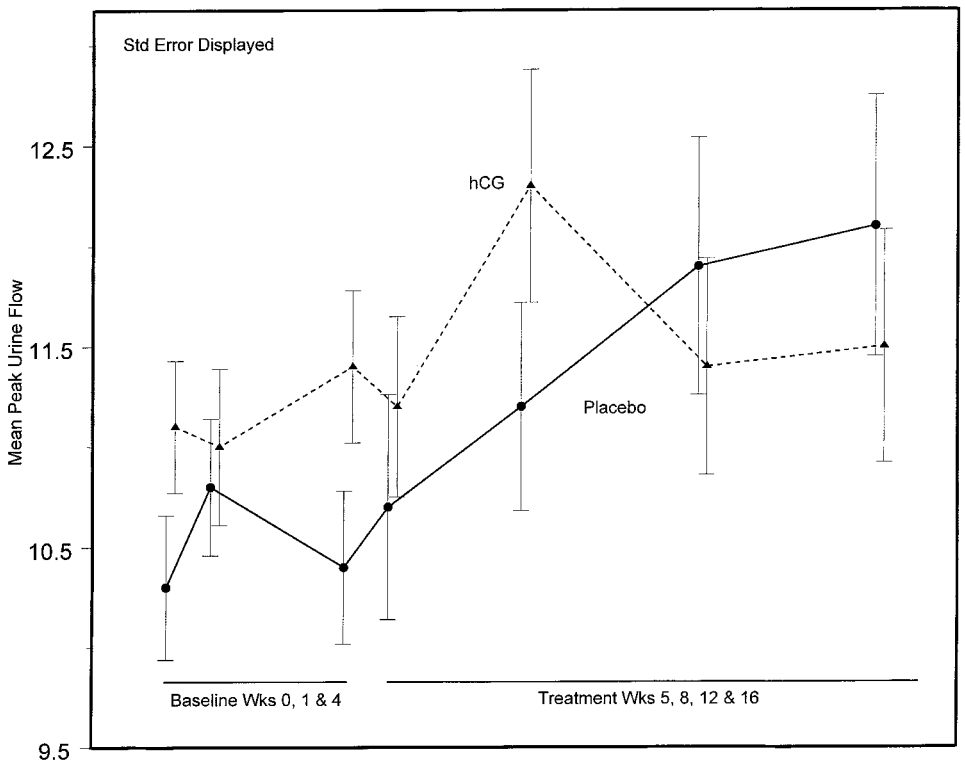

FIG. 3. Qmax for all weeks

or to elevated PSA (14%). Eight individuals (11%) responded to placebo at 28 days.

Adverse events. There were no significant differences in the frequency or severity of adverse events compared with placebo. Table 2 shows select adverse events noted in this trial. Unexplained and interesting findings include decreased libido, elevated serum cholesterol and a 2% erectile dysfunction rate. Mean systolic and diastolic blood pressure for the 2 treatment groups was similar for weeks 4, 5, 8, 12 and 16.

Outcomes and estimation. A total of 101 subjects were randomized to the HCG (53) and placebo (48) treatment groups. Seven subjects withdrew from the study during the randomization period. Subjects on placebo were an average of 3 years older than those on HCG (66.4 vs 63.5 years, $p = 0.019$). For this reason efficacy analyses were done with and without adjustment for age.

Number analyzed. HCG improved AUA scores ($p = 0.0261$) and sexual functioning ($p = 0.0481$) compared with placebo

TABLE 5. *Change from baseline to week 16 in prostate volume and PSA*

Treatment Group*	No. Baseline/ Wk 16	Mean Baseline ± SD	Mean Wk 16 ± SD	Nominal Mean Change Score Statistics ± SD	p Value (Wilcoxon rank sum test)
Prostate vol:					0.686
HCG	51/48	32.8 ± 14.9 Cm^3	31.5 ± 12.2 Cm^3	−1.6 ± 6.8	
Placebo	48/45	35.1 ± 14.9 Cm^3	34.0 ± 12.7 Cm^3	−1.3 ± 9.4	
PSA:					0.997
HCG	51/49	1.7 ± 2.0 Ng/ml	1.4 ± 1.2 Ng/ml	−0.3 ± 1.2	
Placebo	48/44	2.1 ± 1.5 Ng/ml	2.0 ± 1.3 Ng/ml	−0.2 ± 1.1	

* Intent to treat population.

(tables 3 and 4). Statistical significance was maintained when analysis was adjusted for age for AUA scores ($p = 0.0238$) and sexual functioning ($p = 0.0355$). Qmax increased slightly in the HCG and placebo groups but did not attain statistical significance ($p = 0.1340$).

The effect of HCG on AUA scores was evident after 1 week of therapy (week 5) and it achieved a maximum decrease in total AUA score after 4 weeks (fig. 1). The same analysis as described above was performed in all randomized subjects who had a total AUA score of 13 or greater at baseline (fig. 2). The mean change in total AUA score was −6.58 and −3.31 for HCG and placebo, respectively. The average percent improvement in AUA scores was 68% in subjects with mild to moderate prostatic disease and 99% in those with moderate to severe disease (AUA score 13 or greater).

Ancillary analyses. Analysis of the secondary efficacy parameter sexual functioning showed superior sexual functioning (increased SSEQ scores) even after adjustment for age in HCG treated subjects relative to placebo treated subjects ($p = 0.0355$). There was no significant difference in Qmax (fig. 3). There was a slight improvement in peak urine flow in placebo and HCG treated subjects during the active treatment phase of the study. Differences within each treatment and between the treatments appear to be spontaneous and a function of random fluctuation.

PSA, prostate volume and testosterone. Table 5 lists PSA values and prostate volumes in the HCG and placebo study groups. Wilcoxon rank sum statistics were used to generate p values based on the nominal change from weeks 4 to 16 (end of treatment population). There were no significant changes in prostate volume or PSA during the treatment period. Testosterone was not determined since changes in testosterone are thought to occur only with subcutaneous injections of 500 IU or greater of HCG.

DISCUSSION

We assessed the safety and efficacy of relatively low dose HCG for decreasing the lower urinary tract symptoms associated with BPH. HCG administered at a total daily dose of 2 IU for the 3-month study period achieved statistical significance vs placebo for reducing BPH symptoms, as measured by the AUA score. These data compare favorably with those in published reports of the pivotal clinical trials for α1-blockers and type II 5α-reductase inhibitor (figs. 1 and 2).[4] A subanalysis of our data involved all subjects with a total AUA score of 13 or greater. This subanalysis revealed that HCG was responsible for even greater improvement in symptoms in the patient group with severe BPH symptoms (fig. 2). HCG produced statistically significant improvements in sexual function even after stratification for age. There were no HCG induced changes observed in PSA or prostate volume.

An area in which HCG and HCG receptors may have a role in the treatment of prostatitis is the regulation of inflammatory responses. This modulation of the inflammatory response is supported by observations that HCG decreases the proliferation of peripheral monocytes induced by stimulants such as phytohemagglutinin or concanavolin A.[18] Overall in cells and animals treated with HCG there is reported suppression of the production of tumor necrosis factor-$\propto$, interleukin-6 and interleukin-I β in inflamed tissues.[19] Inflammation typically induces proliferation of the surrounding tissues and HCG may also behave as an antiproliferative agent in specific tissues. In BPH and prostatitis cases inflammatory and immune components contribute to hyperproliferation and the resultant symptoms. HCG was well tolerated and it provided a benefit of improvements in symptoms and sexual function in treated subjects. Additional studies are needed to assess if the treatment can also improve other symptoms of the disease.

CONCLUSIONS

Since HCG may act directly or indirectly on the prostate and associated tissues through mechanisms independent of α1-blocker or α-reductase inhibitors, this therapy may provide an alternative and/or complementary role for the treatment of BPH. Based on the positive results in AUA and SSEQ symptomatology scores, and a nonconclusive effect on Qmax, HCG is likely to be focused on relieving the irritative symptomatology of BPH.

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