Lower Urinary Tract

An international, multicentre, randomized double-blind trial is presented. Patients were randomized to treatment with tolterodine, placebo, and two doses of solifenacin. The authors concluded that the two doses of solifenacin improved urgency and other symptoms of the overactive bladder, with an acceptable level of side-effects.

A further phase 3 study into the effect of duloxetine was undertaken to assess whether the previous evidence of efficacy from North America and Europe could be sustained in other parts of the world. In this double-blind placebo-controlled study, the authors found that duloxetine improved continence and quality of life, in keeping with the findings in North America and Europe.

A novel temporary prostatic stent has been evaluated; it looks like the proximal 4–6 cm of a Foley catheter, with a similar proximal balloon to prevent displacement. In this early study it was found to be user-friendly, and to improve symptoms in patients with BOO caused by prostatic enlargement.

Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder

C.R. CHAPPLE, T. RECHBERGER*, S. AL-SHUKRI†, P. MEFFAN‡, K. EVERAERT¶, M. HUANG§ and A. RIDDER° on behalf of the YM-905 Study Group

*Royal Hallamshire Hospital, Sheffield, UK; *Akademia Medcyzna Lublinie, Lublin, Poland; †St. Petersburg Pavlov Medical University, St. Petersburg, Russia; ‡Roundhay Medical Centre, Nelson, New Zealand; ¶University of Ghent, Ghent, Belgium; §Yamanouchi Group Business LLC, Paramus, New Jersey, USA; and °Yamanouchi Europe B.V., Leiderdorp, the Netherlands*

Accepted for publication 20 October 2003

OBJECTIVE

To assess in a phase 3a trial the efficacy of solifenacin succinate, a once-daily oral antimuscarinic agent in development at 5-mg and 10-mg dosage strengths, for the treatment of overactive bladder (OAB)) (Yamanouchi Pharmaceutical Co. Ltd, Tokyo, Japan) compared with placebo in patients with symptoms of OAB, i.e. urgency, incontinence, and frequency, with additional objectives being to assess the safety and tolerability of solifenacin and to compare the efficacy and safety of solifenacin with tolterodine 2 mg twice daily.

PATIENTS AND METHODS

The study was an international, multicentre, randomized, double-blind, tolterodine- and placebo-controlled trial conducted at 98 centres. Adult patients with symptomatic OAB for ≥3 months were eligible; after a single-blind 2-week placebo run-in period patients were randomized equally to a 12-week double-blind treatment with either tolterodine 2 mg twice daily, placebo, solifenacin 5 mg or 10 mg once daily. Efficacy variables included change from baseline in the mean number of urgency, incontinence and urge incontinence episodes, and change from baseline in voids/24 h and mean volume voided/void.

RESULTS

In all, 1281 patients were enrolled, 1081 randomized and 1077 treated; 1033 were evaluated for efficacy. Compared with placebo, the change from baseline (−1.41, −32.7%) in the mean number of urgency episodes per 24 h was statistically significantly lower with solifenacin 5 mg (−2.85, −51.9%) and 10 mg (−3.07, −54.7%; both $P < 0.001$), but not with tolterodine (−2.05, −37.9%; $P = 0.0511$). There was a statistically insignificant decrease in episodes of incontinence with tolterodine (−1.14; $P = 0.1122$) but a significant decrease in patients treated with solifenacin 5 (−1.42; $P = 0.008$) and 10 mg (−1.45; $P = 0.0038$). Compared with placebo (−1.20, −8.1%) the mean number of voids/24 h was significantly lower in patients receiving tolterodine (−1.88, −15%; $P = 0.0145$), solifenacin 5 (−2.19, −17%) and 10 mg (−2.61, −20%; both

$P < 0.001$). The mean volume voided/void was also significantly higher with all three active treatments ($P < 0.001$). Solifenacin was well tolerated; compared with placebo (4.9%), dry mouth (the most common side-effect), mostly mild, was reported in 18.6% of patients receiving tolterodine, 14.0% receiving 5 mg and 21.3% receiving 10 mg solifenacin.

CONCLUSION

Solifenacin 5 and 10 mg once daily improved urgency and other symptoms of OAB, and was associated with an acceptable level of anticholinergic side-effects. Solifenacin demonstrated significantly favourable efficacy to side-effect ratio in treating symptomatic OAB.

KEYWORDS

incontinence, overactive bladder, muscarinic receptor antagonist, drug therapy

INTRODUCTION

Overactive bladder (OAB) has been defined by the International Continence Society as a syndrome comprising the symptoms of urgency, with or without urge incontinence, usually accompanied by frequency and nocturia [1]. Epidemiological surveys indicate that OAB affects 16–22% of American and European adults, with higher prevalence rates in older people [2–4]. In a large population-based prevalence study conducted in six European countries, 54% of patients with symptoms of OAB complained of urgency as a primary symptom [2]. Patients with OAB, including those who remain continent, experience significant decreases in health-related quality of life (QoL) and daily functioning [2,3,5,6]. Compared with age- and gender-matched controls, patients with OAB report more UTIs and a greater risk of being injured in a fall [7]. Not surprisingly, therefore, OAB is being increasingly recognized as a widespread condition of concern, not only to urologists but also to other healthcare professionals, including gynaecologists and primary-care practitioners.

Although treatment approaches to OAB can include behavioural, pharmacological and surgical interventions, pharmacological management remains the mainstay of therapy [8,9]. Of all of the available agents, muscarinic receptor antagonists are the treatment of choice [9]. However, to date the efficacy of many of these agents has been suboptimal in terms of clinical effectiveness (the balance between efficacy and tolerability) and furthermore, there are few data on the control of urgency, as manifested by the voluntary warning time that patients have to reach the toilet, the principal symptom of OAB. As muscarinic receptors are of functional importance in several tissues in addition to the bladder, the utility of antimuscarinic therapy has historically been limited by the maximum tolerable dosage consequent on the adverse effects resulting from generalized muscarinic receptor blockade. Dry mouth is the most common side-effect [9,10], although constipation, drowsiness and blurred vision also occur [9,11]. As OAB follows a chronic course requiring long-term therapy, there is therefore a significant need for new agents with better clinical effectiveness, as demonstrated by better tolerability consequent upon an improved efficacy to side-effect ratio.

Solifenacin succinate (Yamanouchi Pharmaceutical Co. Ltd, Tokyo, Japan) is a once-daily oral antimuscarinic agent in development that shows apparent functional selectivity for bladder over other organs in animal models [12–14]. In preclinical *in vitro* and *in vivo* studies, solifenacin showed relative selectivity for the bladder compared with salivary gland tissue. Solifenacin inhibited carbachol-induced intracellular calcium mobilization in bladder smooth muscle cells more potently than in submandibular gland cells and, in anaesthetized mice and rats, inhibited carbachol-induced increases in bladder pressure more potently than carbachol-induced salivary secretion [12–14]. Additionally, solifenacin showed a greater degree of selectivity for the bladder over salivary gland than tolterodine and oxybutynin in both *in vitro* and *in vivo* animal models [12,14]. This superior bladder selectivity compared with both oxybutynin and tolterodine was the rationale for the clinical development of solifenacin for treating OAB.

Pharmacodynamic measurements of salivary flow in healthy subjects were consistent with the earlier preclinical observations; at therapeutic doses of 5 and 10 mg, the effect of solifenacin on salivary secretion was dose-dependent but similar to that of placebo [15]. Pharmacokinetic studies in healthy subjects showed good oral absorption with a mean time to maximum plasma concentration (t_{max}) of 3–6 h and an extended mean terminal elimination half-life ($t_{1/2}$) that enabled once-daily administration. The maximum plasma concentration of drug (C_{max}) and area under the plasma concentration-vs-time curve were dose-proportional [15–17].

Phase 2 trials in patients with symptomatic OAB have shown statistically significant reductions in voiding frequency and a significant increase in volume voided/void at doses of 5, 10 and 20 mg once daily. Also, the incidence of dry mouth in patients receiving both 5 and 10 mg solifenacin was numerically lower than in patients receiving tolterodine 2 mg twice daily, although this phase-2 study was not adequately powered to allow adequate statistical comparison between active treatments [18].

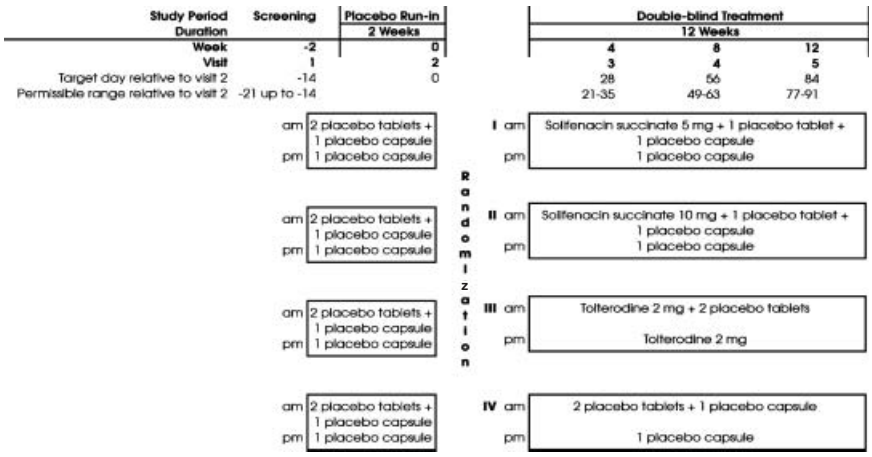
The primary objective of the present phase 3a trial was to assess the efficacy of solifenacin 5 and 10 mg once-daily compared with placebo in a large sample of patients with symptoms of OAB. The secondary objectives were to assess the safety and tolerability of solifenacin 5 and 10 mg once daily, and to compare the efficacy and safety of solifenacin with tolterodine 2 mg twice daily.

PATIENTS AND METHODS

This multicentre, randomized, double-blind, tolterodine- and placebo-controlled phase 3a trial was conducted internationally at 98 centres in accordance with the International Conference on Harmonization-Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The study protocol was approved by the responsible ethical committee at each study site. All patients were informed of the nature and purpose of the study, and written informed consent was obtained before screening.

Men and women aged ≥18 years with symptoms of OAB (including urgency, urge incontinence, or frequency) for ≥3 months were eligible for screening and study enrolment. To be eligible for randomization after the 2-week placebo run-in period (see below), patients had to have had an average frequency of ≥8 voids/24 h and have experienced at least three episodes of urgency and/or three episodes of incontinence during the 3-day voiding diary period (see below). Exclusion criteria included clinically

FIG. 1. Schedule of the overall study design.



significant BOO, a postvoid residual volume of >200 mL, incontinence for which stress was determined to be the predominant factor, presence of a neurological cause for detrusor muscle overactivity, evidence of UTI or bladder stones, previous pelvic irradiation, or previous or current malignant disease of the pelvic organs, any medical condition contraindicating the use of antimuscarinic medication (including narrow-angle glaucoma and urinary or gastric retention), nonpharmacological treatment for OAB including electrostimulation therapy or start of a bladder training programme during the 2 weeks before or during the study, diabetic neuropathy, use of drugs intended to treat incontinence, use of any drugs with cholinergic or anticholinergic side-effects, and participation in a clinical trial within 30 days before study entry. Women of child-bearing potential who were pregnant or nursing, intending to become pregnant during the study, or who were not using reliable contraceptive methods, were ineligible.

STUDY DESIGN

At an initial screening visit (week −2) the patients provided a medical history, and had a physical examination, postvoid bladder ultrasonography, blood and urine laboratory analyses (including urine culture), and an electrocardiogram (ECG). Eligible patients received placebo twice daily (morning and evening) over a 2-week run-in period; during the 3 days before the next visit (week 0), patients recorded in a voiding diary episodes of urgency and incontinence, the times of voiding, volumes voided/void, pad use, and episodes of sleep disturbance. Eligible patients after the run-in period (see above) were randomized equally to 12-week double-blind treatment with either tolterodine 2 mg twice daily, placebo, or solifenacin 5 or 10 mg once daily. To maintain blinding, all patients continued to take medication twice daily (using placebo tablets and capsules as necessary) during the 12-week treatment period (Fig. 1).

EFFICACY ASSESSMENT

Efficacy variables included change from baseline in the mean number of urgency episodes and mean number of all incontinence and urge incontinence episodes. Additional variables included mean number of voids/24 h and changes from baseline in mean voided volume/void. After randomization and the start of the 12-week treatment period patients were evaluated for efficacy every 4 weeks. The voiding diaries were completed for 3 days before each follow-up visit.

SAFETY ASSESSMENT

Adverse events were recorded and categorized by severity and likelihood of causal relationship to study medication. Interval visit safety assessments at weeks 4, 8 and 12 included vital signs, physical examination and adverse event recording. Laboratory screening and an ECG were repeated at the end of the study. The postvoid residual volume was assessed by either bladder ultrasonography or scanning (the same method used for each patient) at the start and finish of the 12-week treatment period.

STATISTICAL ANALYSIS

Based on a projected difference of 1.0 in the change from baseline in voiding frequency/24 h for solifenacin vs placebo, with a SD = 3, a significance level of $\alpha = 0.05$, two-sided, and a power of 90%, 190 evaluable patients per treatment arm were required. To obtain a total of 760 evaluable patients, assuming a discontinuation rate of 20% during the run-in and treatment periods, 1180 patients had to be enrolled.

A hierarchical test procedure was used whereby a comparison of solifenacin 10 mg once daily to placebo was tested at the two-sided 0.05 significance level using the corresponding contrast. If there was statistical significance, comparison of solifenacin 5 mg to placebo was tested at the two-sided 0.05 significance level using the corresponding contrast; this was considered the principal analysis. Continuous variables were summarized using descriptive statistics, and categorical variables described using absolute and relative frequency. Changes from baseline in the primary and secondary efficacy variables were calculated and subjected to ANOVA, including treatment as a fixed factor. There were 98 centres involved in the trial, so centre was included as a random factor. Underlying assumptions of the planned analysis were investigated by inspecting the residual plots. If the assumptions were not met an alternative nonparametric method using the Wilcoxon rank-sum test or log-transformation was advanced for all continuous variables. Summary statistics and CI for tolterodine outcomes were compared with placebo and solifenacin in an exploratory fashion without formal statistical testing.

RESULTS

As shown in Fig. 2, 1281 patients were enrolled in the study, 1081 were randomized and 1077 were treated. The efficacy analysis included all randomized patients who received at least one dose of study drug and who had efficacy data available from the baseline and at least one on-treatment visit (1033). In all, 109 patients (10%) were discontinued before completing the study

because of adverse events (2.9% of all patients) and withdrawal of consent (3.3% of all patients). The highest discontinuation rate was in the placebo group (12%); 99% of patients in the placebo arm, and 93% in the tolterodine 2 mg twice daily, and solifenacin 5 and 10 mg arms had their final (endpoint) efficacy evaluation at week 12.

Table 1 shows the baseline patient demographic characteristics for each treatment group; the four groups were well balanced for all demographic characteristics. The mean age was 56.9–58.1 years; >98% of patients were white and the overall female/male ratio was ≈3 : 1.

The clinical characteristics at baseline are also shown in Table 1. The mean number of voids/24 h was 12.08–12.32 and was similar among the treatment groups. The mean time from the start of symptoms was 57.4–72.6 months. About a third of patients had received previous drug treatment for OAB, and >90% of patients in each group reported incontinence, principally urge incontinence.

EFFICACY

Table 2 shows the change in mean number of urgency episodes/24 h; compared with the change in the placebo group (–33%), there was a small, statistically insignificant decrease in patients treated with tolterodine (–38%; $P = 0.0511$) and a statistically significant decrease in those treated with solifenacin 5 mg (–52%) and 10 mg once daily (–55%; both $P < 0.001$). As shown in Fig. 3a, two-thirds of the effect obtained after 12 weeks of treatment was already evident by 4 weeks, at the first assessments. Direct comparison of solifenacin 5 and 10 mg with tolterodine resulted in estimated differences of –0.791 and –1.015 (95% CI –1.434 to –0.148, and –1.659 to –0.370), respectively.

Table 2 also shows the change in the mean number of urge incontinence and all incontinence episodes per 24 h; compared with changes in the placebo group (–0.62 episodes/24 h) there were statistically insignificant decreases in both urge and general incontinence with tolterodine. There were statistically significant decreases in the number of urge incontinence episodes in patients treated with solifenacin 5 mg (–1.41, $P = 0.002$) and 10 mg (–1.36, $P = 0.0028$). Solifenacin also produced statistically significant reductions in all incontinence

FIG. 2. Disposition of study patients. Enrolled patients received placebo run-in treatment for two weeks. Patients still eligible following placebo run-in were randomized to one of four treatments.

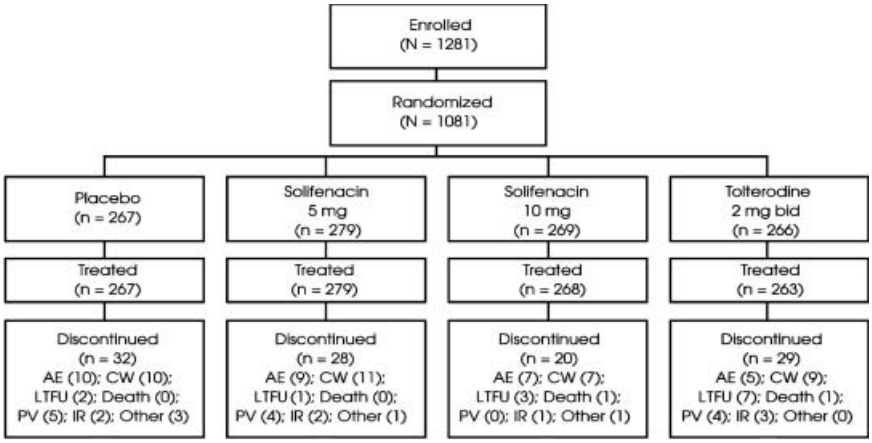


TABLE 1 The patients' demographic and clinical characteristics

Characteristic	Placebo	Solifenacin, mg (once daily) 5	10	Tolterodine 2 mg (twice daily)
No.	253	266	264	250
Demographic				
Mean (SD) age, years	57.8 (13.7)	58.1 (13.4)	57.2 (13.4)	56.9 (12.8)
range	19–82	19–85	19–84	19–79
N (%)				
< 65	168 (66.4)	169 (63.5)	172 (65.2)	172 (68.8)
≥ 65	85 (33.6)	97 (36.5)	92 (34.8)	78 (31.2)
< 75	225 (88.9)	236 (88.7)	241 (91.3)	233 (93.2)
≥ 75	28 (11.1)	30 (11.3)	23 (8.7)	17 (6.8)
Mean (SD) weight, kg	72.6 (14.4)	74.6 (14.3)	75.5 (14.2)	74.8 (14.8)
range	43–130	47–150	42–135	43–129
Gender, n (%) M	60 (23.7)	72 (27.1)	76 (28.8)	50 (20.0)
F	193 (76.3)	194 (72.9)	188 (71.2)	200 (80.0)
Race, n (%)				
White	248 (98.0)	261 (98.1)	260 (98.5)	247 (98.8)
Black	1 (0.4)	2 (0.8)	0	1 (0.4)
Asian	1 (0.4)	2 (0.8)	0	2 (0.8)
Other	3 (1.2)	1 (0.4)	4 (1.5)	0
Clinical				
Mean (SD) no. of voids/24 h	12.20 (4.11)	12.08 (3.86)	12.32 (3.95)	12.08 (3.43)
Type of incontinence, n (%)				
UI only	177 (70.0)	172 (64.7)	162 (61.4)	142 (56.8)
Mixed SI/UI*	59 (23.3)	79 (29.7)	81 (30.7)	90 (36.0)
No incontinence	17 (6.7)	15 (5.6)	20 (7.6)	18 (7.2)
Time from start of symptoms, months				
N	108	120	113	96
Mean (SD)	61. 0 (83. 9)	57. 4 (60. 5)	72. 6 (105. 4)	62. 9 (82. 5)
Prior drug therapy, n (%)				
Yes	83 (32.8)	93 (34.9)	106 (40.1)	77 (30.8)
No	169 (66.8)	172 (64.7)	157 (59.5)	172 (68.8)
Any nondrug therapy	76 (30.0)	92 (34.6)	92 (34.8)	88 (35.2)

*SI, stress incontinence; UI, urge incontinence; *With UI as predominant factor.*

TABLE 2 The change in the mean number of urgency episodes/24 h, incontinence and urge incontinence episodes/24 h, mean voids/24 h and mean volume voided/void

Characteristic	Placebo	Solifenacin, mg (once daily) 5	Solifenacin, mg (once daily) 10	Tolterodine* 2 mg (twice daily)
Urgency episodes/24 h, N	248	264	261	250
Baseline	5.30 (3.92)	5.77 (4.89)	5.82 (4.45)	5.45 (3.87)
Endpoint	3.89 (4.64)	2.93 (4.40)	2.75 (3.80)	3.40 (4.29)
Change from baseline	−1.41 (3.67)	−2.85 (3.74)	−3.07 (3.90)	−2.05 (3.58)
Percent change from baseline	−33	−52	−55	−38
Estimated difference vs tolterodine (95% CI)	–	−0.791 (−1.434, −0.148)	−1.015 (−1.659, −0.370)	–
P	–	<0.001	<0.001	0.0511
Incontinence and urge incontinence episodes/24 h				
Urge incontinence, N	127	113	127	119
Baseline	2.02 (2.50)	2.33 (2.42)	2.14 (2.44)	1.86 (1.54)
Endpoint	1.40 (2.59)	0.92 (1.99)	0.77 (1.82)	0.94 (2.20)
Change from baseline	−0.62 (1.96)	−1.41 (1.74)	−1.36 (2.13)	−0.91 (2.01)
Percent change from baseline	−40	−65	−63	−58
Estimated difference vs tolterodine (95% CI)	–	−0.487 (−0.988, 0.014)	−0.436 (−0.921, 0.048)	–
P	–	0.002	0.0028	0.2390
Incontinence, N	153	141	158	157
Baseline	2.71 (2.83)	2.64 (2.55)	2.59 (2.88)	2.32 (1.94)
Endpoint	1.96 (3.24)	1.22 (2.17)	1.14 (2.22)	1.18 (2.38)
Change from baseline	−0.76 (2.26)	−1.42 (1.82)	−1.45 (2.24)	−1.14 (2.15)
Percent change from baseline	−29	−59	−47	−59
Estimated difference vs tolterodine (95% CI)	–	−0.276 (−0.761, 0.208)	−0.316 (−0.786, 0.154)	–
P		0.008	0.0038	0.1122
Mean voids/24 h, N	253	266	264	250
Baseline	12.20 (4.11)	12.08 (3.86)	12.32 (3.95)	12.08 (3.43)
Endpoint	10.99 (4.21)	9.88 (3.75)	9.70 (3.52)	10.20 (3.71)
Change from baseline	−1.20 (3.26)	−2.19 (2.87)	−2.61 (3.24)	−1.88 (3.00)
Percent change from baseline	−8	−17	−20	−15
Estimated difference vs tolterodine (95% CI)	–	−0.312 (−0.844, 0.219)	−0.737 (−1.269, −0.204)	–
P	–	0.0003	<0.001	0.0145
Mean volume voided/void, mL				
Baseline	143.8 (53.6)	149.6 (54.6)	147.2 (51.2)	147.0 (50.3)
Endpoint	151.2 (55.9)	182.6 (71.7)	186.4 (76.6)	171.4 (67.6)
Change from baseline	7.4 (36.3)	32.9 (47.7)	39.2 (50.5)	24.4 (49.2)
Percent change from baseline	9	25	29	20
Estimated difference vs tolterodine (95% CI)	–	8.4 (0.496, 16.34)	14.8 (6.855, 22.72)	–
P	–	<0.001	<0.001	<0.001

**Tolterodine comparisons were based on exploratory data.*

episodes (5 mg, −1.42, $P = 0.008$; and 10 mg, −1.45, $P = 0.0038$).

Table 2 shows the change in mean number of voids/24 h and the percentage change from baseline in each of the four treatment groups. Compared with the change in the placebo group (1.20, −8%), each of the three active treatments was associated with a statistically significant reduction in the mean number of daily voids. The reduction from baseline with tolterodine 2 mg twice daily was −1.88 (−15%, ($P = 0.0145$). The reduction was greatest in patients treated with solifenacin 10 mg (2.61, −20%) followed by solifenacin 5 mg (2.19, −17%; both $P < 0.001$). As shown in Fig. 3b, two-thirds of the effect obtained by 12 weeks of treatment was already evident at 4 weeks, the first assessment. Direct comparison of solifenacin 5 and 10 mg with tolterodine resulted in estimated differences

of –0.312 and –0.737 (95% CI –0.844 to 0.219, and –1.269 to –0.204), respectively.

Change from baseline in mean volume voided/void is also shown in Table 2; compared with the change in the placebo group (7.4 mL) there were statistically significant increases of 24.4 mL (+20.3%) with tolterodine 2 mg twice daily 32.9 mL (+25.1%) with solifenacin 5 mg once daily, and 39.2 mL (+29.0%; all $P < 0.001$) with solifenacin 10 mg once daily.

SAFETY AND TOLERABILITY

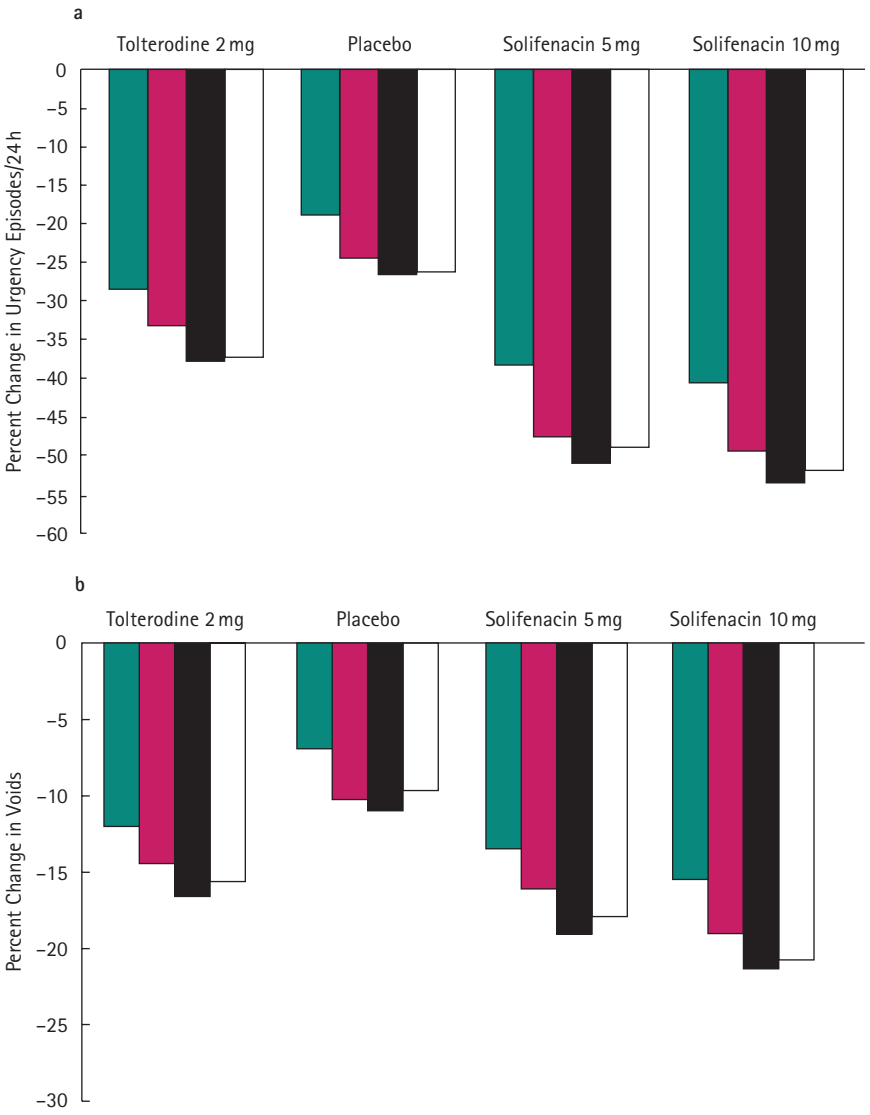
The numbers of patients discontinuing treatment before completing the study are shown in Table 3. The discontinuation rate for adverse events was low and comparable across the four treatment arms. The percentages of patients discontinuing treatment for an adverse event were 3.7% in the placebo group, 3.2% and 2.6% in the solifenacin 5 and 10 mg groups, respectively, and 1.9% in the tolterodine group. Thus, treatment with solifenacin was well tolerated, with a withdrawal rate for adverse events at a level similar to that of placebo.

Table 3 also shows the incidence of major treatment-related anticholinergic side-effects occurring during the study. Among the active treatment groups, the incidence of dry mouth was lowest in patients treated with solifenacin 5 mg (14%) and most of these cases (80%) were mild. Constipation, predominantly mild or moderate in all groups, was reported in 7.2% and 7.8% of patients treated with solifenacin 5 and 10 mg, respectively, in 2.6% of patients treated with tolterodine and in 1.9% of placebo patients. Blurred vision (mild in most cases) was reported in 3.6% of patients receiving solifenacin 5 mg, 5.6% receiving solifenacin 10 mg, 1.5% receiving tolterodine and 2.6% receiving placebo.

There were no clinically relevant changes in vital signs, physical examination findings, laboratory values, postvoid residual volume, or ECG.

QoL data were gathered at several times during the course of this study using a questionnaire validated for incontinence. The authors are aware of the need for QoL outcomes in clinical trials designed to evaluate anticholinergic agents [19]; data from this study will be presented in another paper as part of a pooled analysis of QoL outcomes.

FIG. 3. Percentage change from baseline to endpoint in ***a,*** *the mean number of urgency episodes per 24 h, and* ***b,*** *the mean number of voids/24 h. In each the green bar is week 4, the red bar week 8, the black bar week 12 and the open bar the endpoint. The values are adjusted for the baseline as covariate.*



DISCUSSION

Solifenacin is a once-daily oral antimuscarinic treatment for OAB that has been reported to have preclinical functional selectivity for the bladder over other organs [12–14]. The results of the present study showed that solifenacin at 5 and 10 mg once daily was highly effective at reducing urgency and all the other concomitant symptoms of OAB.

Urgency, which represents an irresistible desire to void is a difficult symptom to both define and quantify. However, it is central to the OAB symptom syndrome, as it leads to increased frequency and urge incontinence, which in turn necessitate substantial modifications in daily activities. Indeed, it must be appreciated that whilst urgency is a symptom of OAB and is reported by more than half of those with this symptom complex [1,2], the pathophysiology of urgency is not well understood. A heightened sense of urgency has been associated with abnormally increased detrusor muscle contractility during bladder filling in patients with OAB [20], and has been associated with a facilitation of detrusor muscle contractility, as measured by maximum external voiding power [21]. The

TABLE 3 The number of patients discontinuing treatment before study completion and the treatment-related major anticholinergic side-effects (1077 patients)

Characteristic	Placebo	Solifenacin, mg (once daily) 5	Solifenacin, mg (once daily) 10	Tolterodine 2 mg (twice daily)	Total
N	267	279	268	263	1077
Discontinuing					
Adverse event	10 (3.7)	9 (3.2)	7 (2.6)	5 (1.9)	31 (2.9)
Consent withdrawal	10 (3.7)	11 (3.9)	7 (2.6)	8 (3.0)	36 (3.3)
Lost to follow-up	2 (0.7)	1 (0.4)	2 (0.7)	6 (2.3)	11 (1.0)
Protocol violation	5 (1.9)	4 (1.4)	0	3 (1.1)	12 (1.1)
Insufficient response	2 (0.7)	2 (0.7)	1 (0.4)	3 (1.1)	8 (0.7)
Patient died	0	0	1 (0.4)	1 (0.4)	2 (0.2)
Other	3 (1.1)	1 (0.4)	1 (0.4)	0	5 (0.5)
Total	32 (12.0)	28 (10.0)	19 (7.1)	26 (9.9)	105 (9.7)
Major side-effects					
Dry mouth	13 (4.9)	39 (14.0)	57 (21.3)	49 (18.6)	
Constipation	5 (1.9)	20 (7.2)	21 (7.8)	7 (2.6)	
Blurred vision	7 (2.6)	10 (3.6)	15 (5.6)	4 (1.5)	

pivotal role of urgency in the OAB symptom complex lends credence to the view that abnormal afferent mechanisms may also be important in the pathogenesis of OAB.

No studies of antimuscarinic agents published to date have evaluated urgency as a primary efficacy variable in patients with OAB. Importantly, both solifenacin doses reduced the mean number of daily episodes of urgency by more than half. These results are in agreement with those of all of the solifenacin phase-2 and -3 studies which showed a consistent amelioration of urgency [22,23]. By contrast, the reduction in the number of urgency episodes with tolterodine was not statistically significantly different from that of placebo in the primary analysis (38% vs 33%; $P = 0.0511$). In a recent systematic literature review of anticholinergic agents and symptoms of OAB [19] no mention is made of urgency as an efficacy variable. In that same review the authors concluded from their meta-analysis that patients taking anticholinergic agents had one fewer episode of incontinence and one fewer void per 48 h. If the present data are extrapolated to 48 h for the purposes of comparison, treatment with solifenacin was associated with about three fewer episodes of incontinence, and four to five fewer voids per 48 h.

Inevitably, reduced urgency and the associated increase in the 'warning time' that bladder emptying is necessary, result in a consequent increase in functional bladder capacity with an increase in volume voided and both reduced frequency and incontinence. Notably, solifenacin at both the 5- and 10-mg doses produced statistically significant reductions in the frequency of daily voids and daily number of urge and all incontinence episodes. Also, both solifenacin 5 and 10 mg were associated with clinically substantial increases in volume voided/void, by 25% and 29%, respectively. Thus, by reducing the symptom of urgency presumably both by reducing abnormal detrusor muscle contractility, and hypothetically by an effect on afferent mechanisms controlling bladder filling, solifenacin effectively increased the functional capacity of the bladder, with a concomitant reduction in voiding frequency and incontinence. Tolterodine 2 mg twice daily produced a smaller increase in volume voided/void, a smaller decrease in the frequency of daily voids, and a statistically insignificant reduction in the number of episodes of incontinence.

Treatment with solifenacin was well tolerated; the discontinuation rate at both solifenacin doses for adverse events was low and comparable with that of placebo. The incidence of dry mouth in patients treated with solifenacin 5 and 10 mg once daily was 14% and 21.3%, compared with 18.6% of patients treated with tolterodine 2 mg twice daily and 4.9% in the placebo group. Although constipation and blurred vision occurred somewhat more often in patients treated with solifenacin than in those treated with tolterodine, most episodes of these side-effects were mild to moderate and rarely led to discontinuation of therapy. The present study used twice-daily tolterodine rather than the once-daily formulation; this was unavoidable as the once-daily formulation was not commercially available when the study was initiated.

In isolated cell preparations from rats and monkeys, solifenacin showed significantly more selectivity for bladder over salivary gland tissue than tolterodine [12]. In anaesthetized rats, solifenacin inhibited carbachol-induced increases in bladder pressure more potently than salivary secretion, with a bladder selectivity ratio of 6.5 (dose required to produce 30% inhibition in salivary gland/dose required to produce 30% inhibition in bladder) compared with a bladder selectivity ratio of 2.4 for tolterodine [14]. Clearly, data from preclinical animal models cannot be directly extrapolated to the clinical situation, and clinical selectivity can only be defined on the basis of clinical data from clinical studies and randomized trials. The results of the present study are consistent with pharmacodynamic observations in phase 1 studies that the effect of solifenacin 5 mg once daily on salivary secretion, and on the visual near point, was similar to that of placebo [15]. The clinical effectiveness of solifenacin 5 mg once daily in terms of both tolerability and efficacy is clear from the present data, as it was associated with the most favourable therapeutic index in the present study. These data are consistent with the suggestion of the relative selectivity of solifenacin for bladder over salivary gland, as reported in the preclinical studies, particularly as shown by the low incidence of dry mouth. Furthermore, some patients may experience greater benefit with a higher dose of this drug, as shown by the efficacy of the 10-mg dose, allowing greater flexibility in drug therapy.

In conclusion, both solifenacin 5 and 10 mg once daily were an effective and well-tolerated new therapy for treating symptomatic OAB. Treatment with solifenacin effectively reduced urgency, with a consequent increase in functional bladder capacity associated with reduced frequency and incontinence, and increased volume voided. As suggested by both preclinical and clinical pharmacodynamic studies, solifenacin treatment was associated with a low

incidence of anticholinergic side-effects, particularly dry mouth, suggesting relative selectivity of solifenacin for bladder over salivary gland. As is true for all antimuscarinic agents, side-effect profiles with solifenacin should be balanced against efficacy outcomes, and low discontinuation rates should provide evidence for a clinically meaningful efficacy/tolerability profile, thereby providing improved clinical effectiveness. With the 5- and 10-mg choice of doses, solifenacin is a safe and effective therapeutic option for patients with OAB.

ACKNOWLEDGEMENTS

This study was undertaken with a research grant from Yamanouchi Pharmaceutical Co., Ltd, Tokyo, Japan.

REFERENCES

1 **Abrams P, Cardozo L, Fall M *et al.*** The standardisation of terminology in lower urinary tract function: report from the Standardisation Sub-Committee of the International Continence Society. *Urology* 2003; **61**: 37–49
2 **Milsom I, Abrams P, Cardozo L *et al.*** How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int* 2001; **87**: 760–6
3 **Stewart W, Herzog R, Wein A *et al.*** Prevalence and impact of overactive bladder in the US. Results from the NOBLE program. *International Continence Society Meeting*, Seoul, Korea 2001 abstract 24
4 **Versi E.** Screening initiative confirms widespread prevalence of overactive bladder in American adults. *Int Urogynecol J* 2001; **12**: S13
5 **Jackson S.** The patient with an overactive bladder – symptoms and quality of life issues. *Urology* 1997; **57** (Suppl. 6A): 18–22
6 **Abrams P, Coyne K, Schmier J *et al.*** Health-related quality of life in continent overactive bladder subjects: early results from the NOBLE program. *International Continence Society Meeting*, Tampere, Finland 2000
7 **Wagner TH, Hu T, Bentkover J *et al.*** Health-related consequences of overactive bladder. *Am J Manag Care* 2002; **8**: S598–607
8 **Madersbacher H.** Denervation techniques. *BJU Int* 2000; **85** (Suppl. 3): 1–6
9 **Chapple CR.** Muscarinic receptor antagonists in the treatment of overactive bladder. *Urology* 2000; **55** (Suppl. 5A): 33–46
10 **Kelleher CJ, Cardozo LD, Khullar V, Salvatore S.** A medium-term analysis of the subjective efficacy of treatment of women with detrusor instability and low bladder compliance. *Br J Obstet Gynaecol* 1998; **104**: 988–93
11 **Yarker YE, Goa KL, Fitton A.** Oxybutynin. A review of its pharmacodynamic and pharmacokinetic properties, and its therapeutic use in detrusor instability. *Drugs Aging* 1995; **6**: 243–62
12 **Hatanaka T, Ukai M, Ohtake A *et al.*** *In vitro* tissue selectivity profile of solifenacin succinate (YM905) for urinary bladder over salivary gland in rats and monkeys. *International Continence Society Meeting*, Florence, Italy 2003 abstract 312
13 **Ikeda K, Kobayashi S, Suzuki M *et al.*** M3 receptor antagonism by the novel antimuscarinic agent solifenacin in the urinary bladder and salivary gland. *Naun-Schmied Arch Pharmacol* 2002; **366**: 97–103
14 **Ohtake A, Hatanaka T, Ikeda K *et al.*** *In vivo* bladder selective profile of solifenacin succinate (YM905) over salivary gland in mice and rats. *International Continence Society Meeting*, Florence, Italy 2003 abstract 297
15 **Smulders RA, Van Alphen WW, Visser JN *et al.*** Multiple dosing with YM905, a novel, bladder-selective antimuscarinic, in healthy men: safety, tolerability, and pharmacokinetics. *International Continence Society Meeting*, Heidelberg, Germany 2002 abstract 439
16 **Smulders RA, Tan HT, Krauwinkel W *et al.*** A placebo-controlled, dose-rising study in healthy male volunteers to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics of single oral doses of YM905. *International Continence Society Meeting*, Heidelberg, Germany 2002 abstract 438
17 **Kuipers ME, Tran DD, Krauwinkel W *et al.*** Absolute bioavailability of YM905 in healthy male volunteers: a single-dose, randomised, two-period crossover study. *International Continence Society Meeting*, Heidelberg, Germany 2002 abstract 437
18 **Chapple CR, Arano P, Bosch JLHR *et al.*** YM905 appears effective and well-tolerated in patients with symptomatic idiopathic detrusor overactivity in a European placebo- and tolterodine-controlled, phase II, dose-finding study. *International Continence Society Meeting*, Heidelberg, Germany 2002 abstract 75
19 **Herbison P, Hay-Smith J, Ellis G, Moore K.** Effectiveness of anticholinergic drugs compared with placebo in the treatment of overactive bladder: systematic review. *Br Med J* 2003; **326**: 841–8
20 **Wein AJ.** Pharmacological agents for the treatment of urinary incontinence due to overactive bladder. *Exp Opin Invest Drugs* 2001; **10**: 65–83
21 **Cucchi A, Siracusano S, Guarnaschelli C, Rovereto B.** Voiding urgency and detrusor contractility in women with overactive bladders. *Neurourol Urodyn* 2003; **22**: 223–6
22 **Cardozo L, Kuzmin I, Lisec ML *et al.*** A double-blind, randomised, placebo-controlled trial with YM905 in symptomatic overactive bladder. *American Geriatric Society Annual Meeting*, Baltimore, Maryland 2003 abstract P74
23 **Gittelman M, Chu F, Klimberg I *et al.*** Two randomized, double-blind, placebo-controlled, fixed-dose, multicenter studies assess the efficacy and safety of daily oral administration of 10 mg YM905 versus placebo in male and female subjects with overactive bladder. *American Urological Association Annual Meeting*, Chicago, Illinois 2003

Correspondence: C.R. Chapple, Department of Urology, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK.
e-mail: c.r.chapple@shef.ac.uk

Abbreviations: **C_{max}**, maximum plasma concentration of drug; **OAB**, overactive bladder; **t_{max}**, mean time to maximum drug concentration; **$t_{1/2}$**, mean terminal elimination half-life; **ECG**, electrocardiogram.