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A MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF TROSPIUM CHLORIDE IN OVERACTIVE BLADDER PATIENTS

Hypothesis / aims of study

Trospium chloride (TCl), a quarternary amine, is an antimuscarinic agent marketed in Europe for the treatment of patients with overactive bladder symptoms. A large US multicenter trial was conducted to determine the effects of TCl when given as 20 mg tablets versus placebo (pbo), twice daily, on urgency, 24-hour frequency, urinary incontinence (UI) and urgency severity associated with overactive bladder, specifically evaluating the time to onset of these parameters over a 12-week treatment period.

Study design, materials and methods

This was a multicenter, parallel, randomized, double-blind, placebo-controlled trial in patients with overactive bladder (OAB). Following a 3-week washout period (1-week for naïve patients) and 7-day baseline diary, 24-hour frequency $\geq$ 10 and $\geq$ 1 UI/day were required for inclusion, prior to receiving either TCl 20 mg bid or pbo for 12 weeks. Interim visits were performed at Weeks 1 and 4. A 7-day diary was collected the week prior to study visits to record each micturition and associated urgency as measured by the IUSS (urgency severity scale), and UI episodes/day, as well as urine volume on Days 6 & 7. Efficacy analyses were done using the intent-to-treat (ITT) with the last observation carried forward (LOCF) data sets. ANOVA models or, where appropriate, rank ANOVA were used. The time to onset of effect was analyzed across study weeks and during Week 1 using reverse stepwise methodology.

Results

A total of 658 patients (trospium 329 patients, placebo 329 patients) were randomly assigned on a 1:1 ratio to receive either trospium chloride 20 mg or placebo twice daily. The patient population was predominantly female (trospium 81.2%; placebo 81.8%) and Caucasian (trospium 86.3%; placebo 91.2%). The mean age in the trospium chloride group was 61.1 years and 61.0 years in the placebo group. The treatment groups were similar with respect to demographic and baseline characteristics.

Patients treated with trospium chloride demonstrated statistically significant reductions in average 24-hour frequency, urinary incontinence episodes, urgency, and urgency severity, while volume voided/void was significantly increased at Weeks 1, 4 and 12 when compared with the placebo group (see Table 1).

The rate of improvement/response over time was analyzed to determine onset of effect across study weeks for effect on 24-hour frequency, urgency severity, urge frequency, volume voided, and frequency of urge incontinence episodes. These analyses show that the onset of effect for TCl for significantly decreasing the 24-hour frequency, decreasing urgency severity, decreasing urge frequency, increasing the volume voided per toilet void, and decreasing the number of daily urge incontinence episodes occur within the first week of treatment. Analysis within the first week of treatment revealed that the effect of trospium was significant on 24-hour frequency and urinary incontinence within the first few days.

The most common adverse events were dry mouth (19.8% TCl vs 5.2% pbo) and constipation (10.9% TCl vs 5.8% pbo). Patients discontinued due to AEs were 7.3% for TCl vs. 4.6% for pbo.

Interpretation of results

The findings for these efficacy variables are consistent with the expected pharmacodynamic effects of TCl. Anticholinergic relaxation of the detrusor muscle would be expected to increase maximum bladder capacity and increase the bladder volume at which the first unstable bladder contraction occurred. This is additionally supported by the clinical effects of decreased 24-hour frequency, decreased urgency severity, decreased urge frequency, increased volume voided, and decreased average daily urge incontinence episodes. While

these effects were evident within the first week, the previously noted parameters, in general, continued to improve at each subsequent study visit week.

Table 1: Summary of results for efficacy endpoints – ITT population

		Mean change from baseline		
		Placebo	Trospium	P-value
Efficacy endpoint	Week	N = 325	N = 323	
24-hour frequency		N = 325	N = 323	
Baseline		13.17	12.94	0.3169
Change from baseline	1	-0.96	-1.42	0.0039
	4	-1.55	-2.34	<0.0001
	12	-1.76	-2.67	<0.0001
Urgency severity score associated with toilet voids[a]		N = 325	N = 323	
Baseline		1.75	1.79	0.4100
Change from baseline	1	-0.01	-0.09	0.0023
	4	-0.04	-0.19	<0.0001
	12	-0.02	-0.21	<0.0001
Volume voided (mL) per toilet void/24 hours[a]		N = 320	N = 319	
Baseline		154.64	154.80	0.9667
Change from baseline	1	6.05	29.23	<0.0001
	4	9.45	39.50	<0.0001
	12	9.44	35.59	<0.0001
Urgency events with toilet voids[a]		N = 325	N = 323	
Baseline		11.81	11.71	0.7158
Change from baseline	1	-0.87	-1.41	0.0033
	4	-1.43	-2.48	<0.0001
	12	-1.53	-2.76	<0.0001
Number of daily urge urinary incontinence episodes[b]		N = 325	N = 323	
Baseline		3.90	3.84	0.9849
% Change from baseline	1	-24.1	-44.8	<0.0001
	4	-40.9	-59.7	<0.0001
	12	-43.6	-65.9	<0.0001

[a] Treatment differences assessed by analysis of variance for ITT:LOCF data set.

[b] Treatment differences assessed by rank analysis of variance for ITT:LOCF data set.

Concluding message

Trospium chloride was found to be effective in treating patients with OAB associated with urge incontinence. TCl significantly improved OAB symptoms within the first few days of beginning treatment and was found to be well tolerated.

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