The efficacy of mirabegron in people living with multiple sclerosis or spinal cord injury: an individual participant data meta-analysis and subgroup analysis

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Introduction

- Medical management of neurogenic lower urinary tract dysfunction (NLUTD) continues to be an important part of guideline-based care for patients with spinal cord injury (SCI) and multiple sclerosis (MS).
- The advent of beta-3 agonists for OAB introduced a new class of medication that could potentially be used to treat patients with NLUTD.
- While authors have published systematic reviews and meta-analyses of clinical trial results, there have been no individual patient data meta-analyses (IPDMA, considered the gold standard of meta-analysis); advantages include:
    - Increased statistical power,
    - Standardized analysis,
    - Improved data quality,
    - Avoidance of ecological bias in subgroup analysis.
- **Our objective** was to conduct an IPDMA using data from the two published randomized placebo-controlled trials of mirabegron in people with MS or SCI, and to conduct exploratory subgroup analyses within this patient population.
- **Our hypothesis** was that mirabegron would result in significant improvements in the measured outcomes.

METHODS

Two relevant studies (Welk et al[1] and Krhut et al[2]) were randomised, multi-center, placebo controlled, trials of mirabegron in people with SCI or MS.

There were two primary outcomes for this study: the change in maximum cystometric capacity and the change in the patient perception of bladder condition (PPBC). Secondary outcomes were the change in the peak pressure of NDO, urodynamic compliance, 24hr pad weight, and an incontinence related quality of life measure (I-QoL).

We conducted three *a priori* exploratory analyses to test hypotheses based on our clinical experiences with mirabegron in NLUTD.

1. Whether mirabegron had significantly better efficacy among people with SCI or MS
2. Whether mirabegron had significantly better efficacy among people with SCI ASIA A (complete SCI) versus SCI ASIA B, C, D or E (incomplete SCI);
3. Whether mirabegron had significantly better efficacy among people with a high SCI (T6 or higher) versus low SCI (T7 or lower)

Statistical analysis

The primary analysis was a comparison between the outcome at the end of study of participants randomised to placebo versus those randomised to mirabegron. Analysis of covariance (ANCOVA) was used to adjust for baseline values. For our exploratory analyses, we used ANCOVA with an interaction term between randomisation status and the subgroup of interest to formally test for a statistically significant differences between subgroups based on randomisation and an exploratory p<0.25 was considered of interest for future study. Marginal means and 95% confidence intervals (CI) are reported.

Comparison of the methodology of the two randomised clinical trials. Characteristics that are the same between the two studies are shown shaded in gray.

	Krhut et al	Welk et al
Study design	Prospective, multicenter randomised, double bind, placebo-controlled trial	
Inclusion	Spinal cord injury (SCI) or Multiple sclerosis (MS)	
	Age 18-65	Age >18
	Neurogenic detrusor overactivity on urodynamics	≥1 urgency/unaware incontinence on voiding diary
		Stable bladder management ≥3 months
Exclusion	Onabotulinum toxin in prior 12 months	
	Indwelling catheters	
	Hypertension (>180/>110mmHg)	
	Urinary tract infection	
		Postvoid residual >250mL and not on IC
		Heart rate >100 bpm
		Prolonged QT interval
		Significant stress incontinence
		Newly modified bladder medications in last 3 months
Protocol	1:1 randomisation	1:1 randomisation, stratified by diagnosis, site and concurrent anticholinergic use
	Anticholinergic medications stopped	Anticholinergic medications continued in some patients (6/32 total)
	Placebo washout 2 weeks	No placebo washout period
	4 week duration	8 week duration
	50mg dose for mirabegron arm	2 weeks at 25mg dose, the 6 weeks at 50mg dose
Primary outcome	Change in cystometric capacity	
Outcomes	Urodynamic parameters	
	24hr pad weights (average of 3 days)	
	Patient perception of bladder condition (PPBC)	
	Incontinence-QoL (I-QoL)	
	Treatment satisfaction visual analogue scale	SF-Qualiveen
		Neurogenic bladder symptom score
		Voiding diary

RESULTS

Brief demographics
- 50 patients were randomized to placebo, and 48 to mirabegron
- Mean age was 48 (12.5) placebo, 44 (11.8) mirabegron.
- 67% were male
- 70% had a SCI, 30% had MS

Primary outcomes from the ANCOVA model.

	n people in analysis [a]	Placebo	Mirabegron	Mean difference	p value
Primary outcomes					
PPBC	98	4.3 (4.0-4.6)	3.5 (3.2-3.7)	-0.8	<0.01
Urodynamic capacity (ml)	98	222 (187-258)	271 (235-307)	+49	0.04
Secondary outcomes					
Peak pressure of NDO (cmH2O)	90	75 (67-82)	55 (47-63)	-20	<0.01
Volume of first NDO (ml)	90	101 (77-125)	191 (166-216)	+90	<0.01
Urodynamic compliance (ml/cmH2O)	80	68 (27-109)	76 (33-119)	+8	0.79
IQOL score [b]	98	46 (42-50)	57 (54-61)	+12	<0.01
24hr pad weight (g)	94	244 (191-297)	165 (113-217)	-79g	0.04

[a] Proportion of patients with missing data 8.2% for peak pressure of NDO and volume of first NDO, 18.4% for urodynamic compliance, and 4.1% for 24hr pad weight.
[b] A higher score represents a better quality of life.

Exploratory analysis of efficacy of mirabegron in SCI versus MS patients

There were 68 patients with SCI, and 30 with MS. **There were no statistical interactions that met our threshold of an exploratory p<0.25 in any of the primary or secondary outcomes.** For the two primary outcomes, the change in PPBC was identical (improvement of 0.8), and the change in urodynamic capacity was +12.3mL for MS patients, and +60.2mL for SCI patients (p=0.40).

Exploratory analysis of efficacy of mirabegron in complete versus incomplete SCI

There were 30 patients with complete SCI, and 38 with incomplete SCI. **The change in the PPBC met our exploratory p<0.25 threshold.** Patients with complete SCI (ASIA A) improved by 0.4 points, however patients with incomplete (ASIA B, C, D E) improved by 1.2 points (p=0.09). Numerical improvements in urodynamic capacity, I-QoL score and 24hr pad weight also favored incomplete SCI patients, however none of these outcomes met our exploratory p value threshold.

Exploratory analysis of efficacy of mirabegron in high versus low SCI

There were 38 patients with high SCI (≥T6), and 29 with low SCI (≤T7). Of those with a high SCI, 17/38 had complete injuries and would in theory be at the greatest risk for autonomic dysreflexia. **The primary outcomes did not meet our exploratory p<0.25 threshold, although numerically favored low SCI.** Patient with low SCI had a greater improvement in their IQOL score (15.4) versus high SCI (7.8, p=0.24).

CONCLUSIONS

- We conducted an IPDMA on the two available placebo controlled randomised trials of mirabegron in people with MS or SCI.
- We demonstrated a significant improvement in people treated with mirabegron compared to placebo in both urodynamic values (such as capacity, peak NDO pressure), patient reported outcome measures (PPBC and I-QoL scores), and incontinence pad weight
- A systematic review of OAB anticholinergic efficacy in NLUTD[3] provides a reference against which to compare mirabegron; the improvement in bladder capacity (+49mL anticholinergics versus +49mL with mirabegron) was similar, however the decrease in peak NDO pressure was more divergent (-38cmH_2O anticholinergics versus -18cmH_2O with mirabegron).
- Our exploratory analysis has confirmed that mirabegron has good efficacy in both people with MS, and those with SCI.
- To our knowledge the impact of SCI lesion completeness and lesion level haven't been explored in other analyses of oral medication for NLUTD.
- While there were some potential signals that our hypotheses that mirabegron has better efficacy in people with lower SCI and incomplete lesions may be valid, prospective study of these groups is necessary before any conclusions can be drawn.

1. Welk B, Hickling D, McKibbon M, Radomski S, Ethans K. A pilot randomized-controlled trial of the urodynamic efficacy of mirabegron for patients with neurogenic lower urinary tract dysfunction. Neurourol Urodynam. 2018 Aug 31;37(8):2810–7.
2. Krhut J, Borovička V, Bílková K, Sýkora R, Míka D, Mokriš J, et al. Efficacy and safety of mirabegron for the treatment of neurogenic detrusor overactivity—Prospective, randomized, double-blind, placebo-controlled study. Neurourol Urodynam. 2018 Mar 31;37(7):2226–33.
3. Madhuvrata P, Singh M, Hasafa Z, Abdel-Fattah M. Anticholinergic drugs for adult neurogenic detrusor overactivity: a systematic review and meta-analysis. European Urology. 2012 Nov;62(5):816–30.