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Department of Urology and Pediatric Urology, Sophia Children's Hospital, Erasmus MC, Rotterdam, the Netherlands

* Correspondence to: F.E.E. van Veen, Department of Urology and Pediatric Urology, Sophia Children's Hospital, Erasmus MC, SK-1270, PO 2040, 3000, CA, Rotterdam, the Netherlands, Tel.: +31(0) 10 703357 f.vanveen@erasmusmc.nl (F.E.E. van Veen)

Keywords

Mirabegron; β 3-Adrenoreceptor agonist; Neurogenic lower urinary tract dysfunction; Urodynamics; Urinary incontinence; Pediatrics

Abbreviations

AM, Antimuscarinic; BC, Bladder compliance; BoNT-A, Onabotulinum Toxin-A injection; CIC, Clean Intermittent Catheterization; NDO, Neurogenic Detrusor Overactivity; EFP, End-filling detrusor pressure; MCC, Maximum cystometric capacity; NLUTD, Neurogenic Lower Urinary Tract Dysfunction; VUDS, Video-urodynamic study; VUR, Vesicoureteral reflux

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Long-term beneficial effects of mirabegron in pediatric patients with therapy-refractory neurogenic lower urinary tract dysfunction

Felice E.E. van Veen^{*}, Martje Schotman, Lisette A. 't Hoen, Bertil F.M. Blok, Jeroen R. Scheep

Summary

Introduction

Neurogenic lower urinary tract dysfunction (NLUTD) in children can cause renal failure and urinary incontinence if not treated sufficiently. Anti-muscarinics (AM) and intradetrusor botulinum toxin injections (BoNT-A) with clean intermittent catheterization (CIC) are widely used treatment options for children with NLUTD. However, a considerable number will become refractory to these treatment options. This study aimed to evaluate the efficacy and long-term outcomes of mirabegron in children with NLUTD as an add-on and as a stand-alone treatment.

Material and methods

Patients under 18 years of age with NLUTD who were refractory to AM and/or BoNT-A and were treated with mirabegron 50 mg were retrospectively studied. Mirabegron was either used as monotherapy or in addition to AM and/or BoNT-A. Video-urodynamic studies (VUDSs) were performed before and after treatment with mirabegron. Changes in video-urodynamic parameters, the need for other NLUTD therapy during follow-up, patient-reported side effects, and urinary incontinence were outcomes of interest.

Results

A total of 34 patients with NLUTD were included. All patients were on CIC and the median age was 13.1 years (IQR 15.9–10.3). Median follow-up was 31.4 months (IQR 57.4–11.4). Bladder compliance improved by 89.9%, from 14.9 to 28.3 ml/cm H₂O (p-value < 0.001). Maximum cystometric capacity, end-filling detrusor pressure, volume at first detrusor overactivity, vesicoureteral reflux, and urinary incontinence significantly improved after mirabegron. The add-on therapy group showed more significant improvements in video-urodynamic outcomes compared to the monotherapy group. The median time of requiring other NLUTD therapy was 25.5 months (IQR 39.8–14.8). None of the included patients reported side effects.

Conclusions

Mirabegron is an effective treatment for children with therapy-refractory NLUTD with an average efficacy of 2 years after which additional therapy is required. Despite the retrospective character of this study, our results confirm the beneficial effect of mirabegron in children with therapy-refractory NLUTD, in particular when mirabegron is used as add-on therapy in those with low-compliance bladders.

Summary Table Video-urodynamic outcomes after mirabegron (n = 34).

Urodynamic parameter	Pre-mirabegron	Post-mirabegron	p value
MCC, ml	297.1 (138.1)	390.6 (156.0)	<0.001
Bladder compliance, ml/cm H ₂ O	14.9 (12.3)	28.3 (17.2)	<0.001
EFP, cm H ₂ O	30.1 (16.9)	20.8 (12.9)	<0.001
Volume at first NDO, ml*	155.9 (56.1)*	245.0 (121.5)*	0.029
Peak pressure of NDO, cm H ₂ O*	50.1 (32.0)*	49.9 (49.0)*	0.807
NDO (%)	14 (41.2)	12 (35.3)	0.500
VUR (%)	7 (20.6)	1 (2.9)	0.031
Bladder trabeculation (%)	25 (73.5)	19 (55.9)	0.070

MCC = maximum cystometric capacity, EFP = end filling detrusor pressure, NDO = neurogenic detrusor overactivity, VUR = vesicoureteral reflux. *n = 14.

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Introduction

In pediatric patients, neurogenic lower urinary tract dysfunction (NLUTD) is often caused by congenital anomalies such as myelomeningocele or caudal regression syndrome. In NLUTD the innervation of the bladder and/or external sphincter is disturbed, which may lead to neurogenic detrusor overactivity (NDO) or detrusor-sphincter dyssynergia. Consequently, if children with NLUTD are not treated sufficiently, they may suffer from urinary incontinence, urinary tract infections, vesicoureteral reflux, and ultimately renal failure. Generally used treatment options for NLUTD are clean intermittent catheterization (CIC) with antimuscarinics (AM) and intradetrusor botulinum toxin-A injections (BoNT-A) (e.g. abobotulinumtoxinA or OnabotulinumtoxinA) [1]. The therapy compliance for AM is poor due to undesirable side effects, including dry mouth, constipation, dry eyes, and potential cognitive changes [2–4]. In addition, BoNT-A is an invasive treatment for children that requires repeated interventions under anesthesia. Eventually, a considerable number of patients become refractory to AM and BoNT-A [5]. After this, complex surgery such as an augmentation cystoplasty may follow as a last resort [6]. Mirabegron is a relatively new β_3 -adrenoreceptor agonist for the treatment of NDO. It has proven effective in the treatment of overactive bladder (OAB) and NDO in adults and has a favorable side-effect profile [7–9]. Mirabegron is recently approved by the US Food and Drug Administration for the treatment of NDO in pediatric patients [10]. However, data on pediatric patients are limited. Only three studies have evaluated mirabegron in children with NLUTD [11–13]. These studies showed improvement in urodynamic parameters and clinical outcomes. Mirabegron is, therefore, a promising treatment option for children with NLUTD and may reduce or delay invasive augmentation ileocystoplasty. However, to date, there are no data on the long-term efficacy of mirabegron in these patients. Therefore, we aimed to evaluate the efficacy and long-term outcomes of mirabegron in children with therapy-refractory NLUTD as an add-on and as a stand-alone treatment.

Material and methods

Study population

Pediatric patients who had undergone a video-urodynamic study (VUDS) at the Sophia Children's Hospital of the Erasmus Medical Center between June 2017 and December 2022 were identified from the electronic patient records (EPR). Patients under 18 years of age with NLUTD who were treated with mirabegron were deemed eligible. Patients were included if they were refractory to AM and/or BoNT-A, had undergone VUDS before and after treatment with mirabegron, and had received mirabegron for at least one month. Patients were excluded if they had undergone prior genitourinary reconstruction, were using indwelling catheters, or if VUDS had been performed more than one year before the start of mirabegron. Patients included in this

study were divided into two groups: the add-on and the monotherapy group.

Procedures

This study retrospectively reviewed EPRs to compile the following data: demographic data, underlying neurological disorder, previous therapy before mirabegron, the dosage of mirabegron, urinary incontinence, side effects, video-urodynamic parameters before and after treatment, need for additional NLUTD therapy (i.e. additional AM, BoNT-A, or bladder augmentation) during follow-up, reason for additional NLUTD therapy (i.e. urodynamic deterioration or increased incontinence), and last date of follow-up. Patients received mirabegron if they were refractory to AM alone or AM and BoNT-A. This was defined as a lack of efficacy (urodynamic deterioration or increased incontinence), despite receiving the maximum tolerable dose of AM and/or BoNT-A. Patients also received mirabegron if they experienced side effects of AM and/or BoNT-A. The previously prescribed AM were oral oxybutynin, solifenacin, tolterodine, or intravesical oxybutynin. Children weighing at least 35 kg received 50 mg mirabegron daily and those weighing between 28 and 35 kg received 50 mg mirabegron every other day (controlled-released), as 25 mg tablets were not available in The Netherlands. The blood pressure was checked before the start of mirabegron treatment. Mirabegron was either used as monotherapy or in addition to AM and/or BoNT-A. Pre-VUDS was performed before the start of mirabegron treatment and post-VUDS was performed after at least one month of mirabegron treatment. VUDSs were performed according to the International Children's Continence Society (ICCS), with a 7-Fr transurethral double-lumen catheter and an 8-Fr rectal pressure sensor [14]. The bladder was filled with radiographic contrast at room temperature with filling rates of 10% of expected or known bladder capacity (mL/min). X-ray was used simultaneously to image the urinary tract. Patients with symptomatic urinary tract infections did not undergo VUDS. The following video-urodynamic parameters were evaluated: maximum cystometric capacity (MCC, ml), bladder compliance (BC, ml/cm H₂O), end-filling detrusor pressure (EFP, cm H₂O), bladder shape (e.g. normal or trabeculation), vesicoureteral reflux (VUR) and if NDO present; volume at first NDO (ml) and peak pressure of NDO (cm H₂O). BC was calculated from the pressure rise (cm H₂O) between the start and end of filling, taking into account any detrusor overactivities and artifacts [15]. All VUDSs were reassessed by two urologists following the International Continence Society guidelines [16].

Ethical approval was granted by the Institutional Review Board of the Erasmus University Medical Center, Rotterdam, the Netherlands (MEC-2022-0195).

Study outcomes

The primary outcome was to evaluate changes in BC after treatment with mirabegron. Secondary outcomes included changes in other video-urodynamic parameters (MCC, EFP, VUR, bladder shape, NDO). The long-term efficacy of

mirabegron was evaluated by the need for other NLUTD therapy (i.e. additional AM, BoNT-A, or bladder augmentation) during follow-up due to clinical or urodynamic deterioration. In addition, patient-reported side effects and urinary incontinence were investigated.

Statistical analysis

Statistical analyses were performed in SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Continuous data were presented as means with standard deviations (SDs) and categorical data as frequencies with percentages. The normality of distribution was assessed using the Shapiro–Wilk W test. Differences in urodynamic parameters were evaluated using the paired T-test (if normally distributed) or the Wilcoxon sign-ranked test (if not normally distributed) for continuous data. The McNemar test was used for categorical data. The analysis distinguished between the add-on and monotherapy group. A sub-analysis of low-compliance bladders was made with a compliance <12.5 ml/cm H₂O [17]. p-value <0.05 was considered statistically significant and all tests were two-sided.

Results

A total of 287 pediatric patients underwent VUDS between June 2017 and December 2022, of whom 102 patients had used mirabegron and were assessed for eligibility. Of these patients, 62 were excluded due to: no neurogenic bladder (n = 23), no VUDS before and after mirabegron treatment (n = 29), instantaneously started with mirabegron combination therapy (n = 8), and ileocystoplasty (n = 2). Forty patients were eligible for inclusion, of whom 6 children had discontinued mirabegron treatment, due to side effects (n = 5) and increased incontinence (n = 1). This resulted in no post-VUDS, so these patients were excluded. A total of 34 patients with NLUTD who received mirabegron for at least one month were included in this study. The patient characteristics are listed in Table 1. All patients performed CIC and the median age was 13.1 years (IQR 15.9–10.3). The median interval between the start of mirabegron treatment and post-VUDS was 6.0 months (IQR 10.6–3.8). The median interval between pre-VUDS and post-VUDS was 9.1 months (IQR 11.8–4.4). Nineteen patients used mirabegron as add-on therapy and 15 patients used mirabegron as monotherapy. There were no differences in patient characteristics between those two groups.

Video-urodynamic outcomes

Urodynamic data are reported in Table 2A. MCC significantly increased by 31.5%, from 297.1 (SD 138.1) to 390.6 ml (SD 156.0) (p-value<0.001). Bladder compliance improved by 89.9%, from 14.9 (SD 12.3) to 28.3 ml/cm H₂O (SD 17.2) (p-value<0.001) and EFP decreased by 30.9%, from 30.1 (SD 16.9) to 20.8 cm H₂O (SD 12.9) (p-value<0.001). Also, the incidence of VUR significantly decreased from seven patients (20.6%) to one patient (2.9%) (p = 0.031). Of these seven patients, four patients

Table 1 Patient characteristics.

Parameter	Patients (n = 34)
Sex (%)	
Female	20 (58.8)
Male	14 (41.2)
Neurogenic cause (%)	
MMC	20 (58.8)
Caudal regression syndrome	5 (14.7)
Spinal cord injury	4 (11.8)
LMMC	3 (8.8)
Juvenile MS	1 (2.9)
Transverse myelitis	1 (2.9)
Therapy before mirabegron (%)	
AM	19 (55.9)
AM and BoNT-A	15 (44.1)
Mirabegron dosage (%)	
50 mg every other day	4 (11.8)
50 mg daily	30 (88.2)
Mirabegron therapy type (%)	
Monotherapy	15 (44.1)
Add-on AM	14 (41.2)
Add-on BoNT-A	4 (11.8)
Add-on AM and BoNT-A	1 (2.9)
Median age at start mirabegron, years (IQR)	13.1 (15.9–10.3)
Median time between start mirabegron and post-VUDS, months (IQR)	6.0 (10.6–3.8)
Median time between pre-VUDS and post-VUDS, months (IQR)	9.1 (11.8–4.4)

MMC = meningocele, LMMC = lipomyelomeningocele, MS = multiple sclerosis, AM = antimuscarinics, BoNT-A = intradetrusor OnabotulinumtoxinA, VUDS = video-urodynamic study.

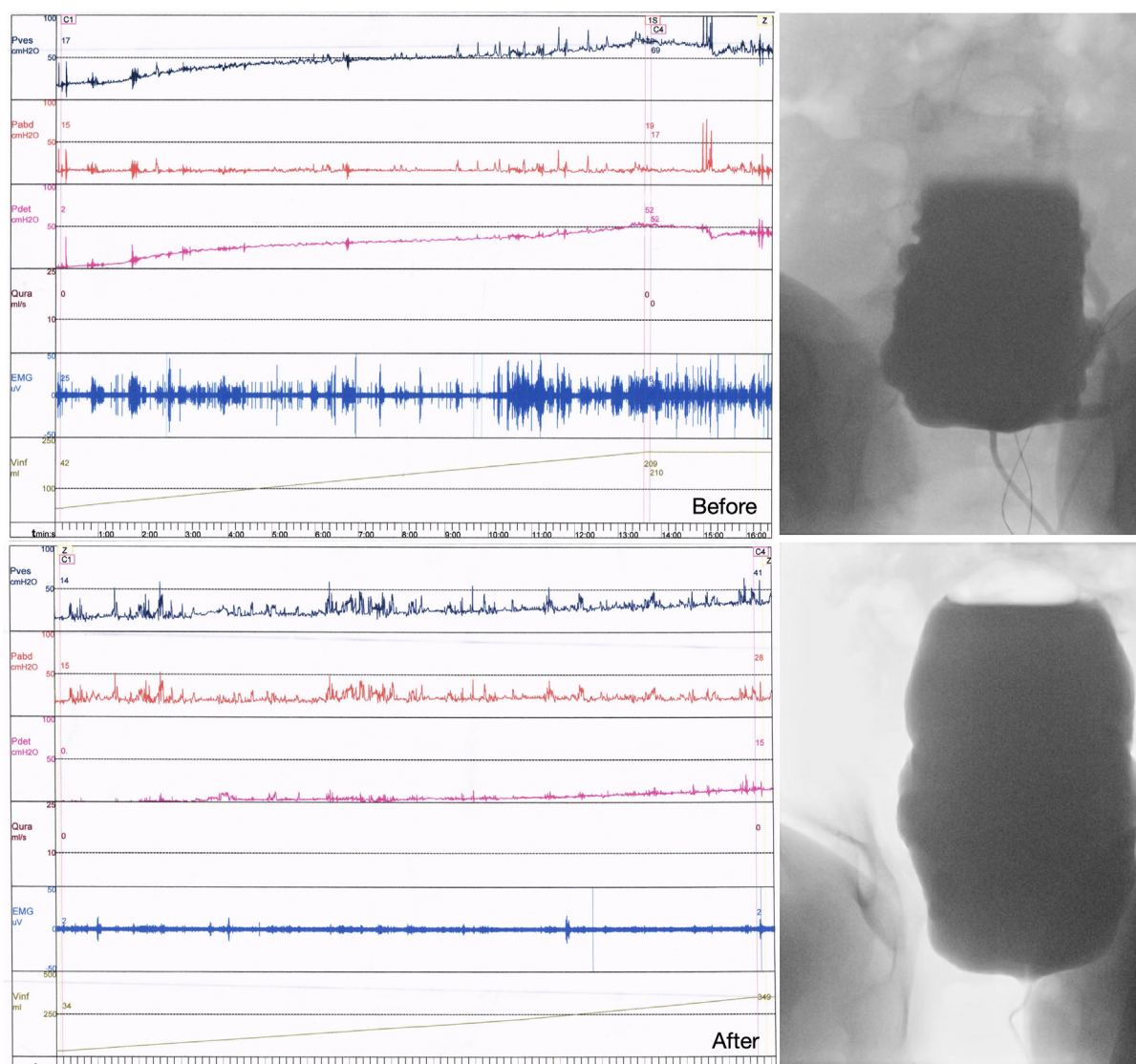
had VUR grade 1, two patients had VUR grade 3, and one patient had VUR grade 4. After mirabegron treatment, VUR grade 3 remained stable in one case and VUR disappeared completely in all other cases. For NDO, only volume at first NDO showed a significant difference, whereas peak pressure NDO did not.

A sub-analysis of 20 children with low compliance bladders showed an even greater improvement in urodynamic parameters after mirabegron administration (Table 2A). The MCC increased by 44.4%, from 283.4 (SD 123.0) to 409.2 ml (SD 134.8) (p-value<0.001), BC improved by 201.5%, from 6.6 (SD 2.5) to 19.9 ml/cm H₂O (SD 12.4) and EFP decreased by 35.2%, from 42.6 (SD 8.6) to 27.6 cm H₂O (SD 11.6). In 14 children with no low-compliance bladder, only BC improved significantly by 51.5%, from 26.6 (SD 11.1) to 40.3 (16.3) (p = 0.035). Fig. 1 shows an original trace of a VUDS before and after mirabegron add-on therapy in a patient with a low-compliance bladder. A separate analysis of the add-on therapy group showed improvement in MCC, BC, EFP and peak pressure of NDO. As opposed to the monotherapy group where there was only a significant difference in BC (Table 2B).

Table 2 Video-urodynamic outcomes after mirabegron: A) total and low-compliance bladder patients. B) add-on and monotherapy patients.

A)	Total (n = 34)			Low-compliance bladder (n = 20)			
	Urodynamic parameter	Pre-mirabegron	Post-mirabegron	p value	Pre-mirabegron	Post-mirabegron	p value
	MCC, ml	297.1 (138.1)	390.6 (156.0)	<0.001	283.4 (123.0)	409.2 (134.8)	<0.001
	Bladder compliance, ml/cm H ₂ O	14.9 (12.3)	28.3 (17.2)	<0.001	6.6 (2.5)	19.9 (12.4)	<0.001
	EFP, cm H ₂ O	30.1 (16.9)	20.8 (12.9)	<0.001	42.6 (8.6)	27.6 (11.6)	<0.001
	Volume at first NDO, ml	155.9 (56.1)*	245.0 (121.5)*	0.029	154.2 (50.2) ^o	275 (120.2) ^o	0.043
	Peak pressure of NDO, cm H ₂ O	50.1 (32.0)*	49.9 (49.0)*	0.807	33.5 (21.5) ^o	24.1 (13.2) ^o	0.138
	NDO (%)	14 (41.2)	12 (35.3)	0.500	6 (30.0)	6 (30.0)	1.000
	VUR (%)	7 (20.6)	1 (2.9)	0.031	7 (35.0)	1 (5.0)	0.031
	Bladder trabeculation (%)	25 (73.5)	19 (55.9)	0.070	18 (90.0)	14 (70.0)	0.125
B)	Add-on therapy (n = 19)			Monotherapy (n = 15)			
	Urodynamic parameter	Pre-mirabegron	Post-mirabegron	p value	Pre-mirabegron	Post-mirabegron	p value
	MCC, ml	302.2 (137.6)	444.2 (156.0)	<0.001	290.7 (143.3)	322.7 (131.4)	0.195
	Bladder compliance, ml/cm H ₂ O	9.9 (6.2)	26.9 (16.2)	<0.001	21.1 (15.2)	30.1 (18.9)	0.017
	EFP, cm H ₂ O	36.6 (14.2)	22.4 (10.5)	0.002	21.9 (16.9)	18.8 (15.6)	0.222
	Volume at first NDO, ml	168.3 (70.0) [^]	296.3 (138.0) [^]	0.109	146.6 (45.9) [~]	219.4 (113.0) [~]	0.141
	Peak pressure of NDO, cm H ₂ O	43.8 (20.7) [^]	19.8 (19.3) [^]	0.028	54.9 (39.2) [~]	72.5 (53.2) [~]	0.028
	NDO (%)	6 (33.3)	4 (22.2)	0.500	8 (53.3)	8 (53.3)	1.000
	VUR (%)	6 (33.3)	1 (5.6)	0.063	1 (6.7)	0 (0.0)	1.000
	Bladder trabeculation (%)	15 (78.9)	10 (52.6)	0.063	10 (66.7)	9 (60.0)	1.000

MCC = maximum cystometric capacity, EFP = end filling detrusor pressure, NDO = neurogenic detrusor overactivity, VUR = vesicoureteral reflux. *n = 14, ^on = 6, [^]n = 6, [~]n = 8.



This is an example of video-urodynamic changes in a 8-year old girl with MMC who had a low-compliance bladder with VUR grade 1 during intravesical oxybutynin alone. After 6 months of mirabegron add-on therapy VUDS improved significantly: MCC improved from 210 to 349 ml, EFP improved from 45 to 15 cm H₂O, BC improved from 4.67 to 23.3 ml/cm H₂O, and VUR disappeared completely.

Fig. 1 Video-urodynamic changes after 6 months of mirabegron add-on therapy in a low compliance bladder.

Clinical outcomes

Thirty-one patients (91.2%) experienced incontinence at enrollment. After mirabegron administration 12 patients (35.3%) were completely dry and 11 patients (32.4%) experienced improvement of incontinence. Incontinence remained stable in seven patients (20.6%) and increased in one patient (2.9%). These incontinence outcomes were significantly different before and after treatment with mirabegron ($p < 0.001$).

None of the included patients reported side effects. However, five patients were excluded because they discontinued mirabegron due to side effects and therefore no post-VUDS were made. The following side effects were described: palpitations ($n = 3$), nausea ($n = 1$), and fatigue ($n = 1$).

Long-term outcomes

Long-term outcomes are reported in Table 3. The median time of follow-up was 31.4 months (IQR 57.4–11.4). Twenty-one (61.8%) patients needed other NLUTD therapy during follow-up, of whom seven (20.6%) patients received additional AM, 6 (17.6%) patients started with additional BoNT-A, five (14.7%) patients started with additional AM combined with BoNT-A, and three (8.8%) patients underwent augmentation cystoplasty. Almost all patients (93.3%) of the monotherapy group needed other NLUTD therapy during follow-up. This is in contrast to 36.8% of the add-on therapy group. Three patients that underwent augmentation cystoplasty had used mirabegron as add-on therapy to AM and BoNT-A, and the median time of requiring augmentation cystoplasty was 21.9 months. The median

Table 3 Long-term efficacy outcomes of mirabegron.

Parameter	Patients (n = 34)
Require other NLUTD therapy (%)	
No	13 (38.2)
AM	7 (20.6)
BoNT-A	6 (17.6)
AM + BoNT-A	5 (14.7)
Augmentation cystoplasty	3 (8.8)
Reason require other NLUTD therapy (%)*	
Urodynamic deterioration	16 (76.2)
Increase urinary symptoms	5 (23.8)
Median time of follow-up, months (IQR)	31.4 (57.4–11.4)
Median time to require other NLUTD therapy, months (IQR)*	25.5 (39.8–14.8)

NLUTD = neurogenic lower urinary tract dysfunction, AM = antimuscarinics, BoNT-A = intradetrusor OnabotulinumtoxinA, *n = 21.

time of requiring other NLUTD therapy was 25.5 months (IQR 39.8–14.8).

Discussion

Pediatric patients with NLUTD represent a challenging treatment group, due to changes in bladder function that can occur throughout their lives. These children are commonly treated with CIC and pharmacological suppression of detrusor overactivity to protect the upper urinary tract. When conservative treatment fails, the combination of high bladder pressure and vesicoureteral reflux may necessitate invasive therapy at a very young age in this population.

Mirabegron, a β_3 -adrenoreceptor agonist, has been developed for the treatment of overactive bladder and is recently approved by the US Food and Drug Administration for the treatment of neurogenic detrusor overactivity in pediatric patients [10]. In the present study, we investigated the efficacy and long-term outcomes of mirabegron in children with therapy-refractory NLUTD.

The results of our study indicate that mirabegron is an effective treatment for children with therapy-refractory NLUTD. Both clinical and video-urodynamic outcomes (including MCC, BC, EFP, peak pressure of NDO, and VUR) showed significant improvement after mirabegron treatment. These findings are similar to those reported by previous studies. Park et al. retrospectively studied the efficacy of mirabegron in 66 children with spina bifida who were refractory to AM [11]. Patients received 50 mg mirabegron daily for an average of 10 months and their results showed improvements in MCC, BC, and incontinence. There was no significant difference in involuntary detrusor contraction. Moreover, Sager et al. evaluated the use of mirabegron as an adjuvant treatment in 37 children with NLUTD who were refractory to AM and/or BoNT-A [12]. Mirabegron 25 mg/day was prescribed and their results

showed improvements in MCC, EFP, and incontinence after three months. The effect of NDO was controversial. Most recently, Baka-Ostrowska et al. included 68 pediatric patients with non-therapy-refractory NDO in their open-label phase III study with a follow-up of one year [13]. They reported that mirabegron monotherapy of 25 mg or 50 mg/day was effective in improving MCC, EFP, BC, and incontinence. In addition, they found a significant increase in bladder volume until first detrusor contraction, which was also found in our observations. The above-mentioned studies are recently summarized in a systematic review with a meta-analysis suggesting that mirabegron improved MCC by an average of 100 ml and BC by 9.8 ml/cm H₂O in children with NLUTD [18]. These outcomes are comparable to our results, which showed an average improvement of 93.5 ml of the MCC and 13.4 ml/cm H₂O of BC.

In our study, mirabegron was used as monotherapy or in addition to AM and/or BoNT-A. We found that mirabegron add-on therapy was more effective compared to monotherapy in terms of MCC, BC, EFP, and peak pressure of NDO. In the long term, almost all patients (93.3%) with monotherapy required additional NLUTD therapy during follow-up and mirabegron alone was not sufficient. Park et al. observed no difference in urodynamic outcomes between add-on and monotherapy [11], except for NDO, which improved only with mirabegron add-on therapy. Moreover, Sager et al. showed a greater reduction in EFP with combination therapy of mirabegron and BoNT-A [12]. Thus, one could hypothesize a synergistic effect of the combination of mirabegron and AM or BoNT-A in the treatment of NLUTD. One possible explanation is that mirabegron has a different mechanism of action than antimuscarinic drugs. Mirabegron induces detrusor muscle relaxation by binding β_3 -adrenergic receptors in the urinary bladder, resulting in relaxation of the bladder. Whereas AM competitively inhibits acetylcholine binding to M3 receptors of the detrusor muscle and avoid instinctive contractions of the bladder. Also, AM inhibits potentially urothelial sensory receptors and decreases afferent nerve activity [19]. Thus, it can be hypothesized that simultaneous targeting of two separate molecular mechanisms involved in the regulation of bladder muscle activity can result in a synergistic effect on alleviating symptoms associated with NLUTD. This approach might be particularly beneficial in difficult-to-treat patients, such as those who are therapy-refractory to AM and/or BoNT-A and have a low-compliance bladder. Furthermore, since deterioration of bladder compliance in myelodysplastic patients is attributed to fibrotic changes in the bladder wall, it can be hypothesized that mirabegron may also have anti-fibrotic effects. Research in mice has shown that cardiac β_3 -adrenergic receptors are involved in the development of fibrosis in response to hemodynamic stress by modulating nitric oxide and oxidant stress-dependent paracrine signaling to fibroblasts [20]. The researchers suggest that a specific β_3 -adrenoreceptor agonist may provide a novel therapeutic modality to prevent cardiac fibrosis. The same theory could be extended to the β_3 -adrenergic receptors of the urinary bladder, which could explain the even greater effect of mirabegron on low-compliant bladders.

To our knowledge, this is the first study that evaluated the long-term (>1 year) efficacy of mirabegron in children with NLUTD. We found a median treatment efficacy of 2 years, after which other NLUTD therapy was required due to urodynamic deterioration or an increase in urinary symptoms. This suggests that mirabegron may delay the use of BoNT-A or invasive augmentation ileocystoplasty in young NLUTD patients, which often causes high levels of anxiety and distress in children. By delaying invasive augmentation ileocystoplasty until older age, they may be able to cope with it more easily.

Baka-Ostrowska et al. reported that the efficacy of mirabegron persisted over 52 weeks of treatment with similar magnitude of treatment effects at weeks 24 and 52 [13]. But they used mirabegron in patients who were not therapy-refractory to AM and/or BoNT-A. Moreover, almost all studies with adult patients had a short follow-up of 6–12 weeks [18,21]. Only one retrospective study by Krebs et al. had a one-year follow-up in which treatment with mirabegron was effective in patients with chronic NLUTD [22].

Although mirabegron has been shown to be well-tolerated by NLUTD patients, this drug may affect the cardiovascular system. In our population, we monitored blood pressure before and after starting mirabegron in order to prevent hypertension complications. No severe side effects of mirabegron had been observed. However, 5 of 102 patients who used mirabegron and were screened for eligibility experienced mild side effects (palpitations, nausea, and fatigue), which disappeared immediately after discontinuation of mirabegron. Previous studies on NLUTD children have demonstrated low complication rates (8.3% and 0.73%), with hypertension, constipation, and dizziness being the most common [18]. Furthermore, research by Krhut et al. found no significant differences between mirabegron and a placebo group in terms of cardiovascular safety [23]. Altogether, these and our findings suggest that mirabegron is a safe option for the treatment of NLUTD in pediatric patients.

The limitations of this study are its retrospective character and small sample size. However, objective video-urodynamic outcomes were used, which reduces the chance of any bias. In return, this is the first study that evaluated the long-term outcomes of mirabegron in NLUTD children and that examined the effect of mirabegron on the bladder shape, and VUR by using VUDS. This illustrated the beneficial effects of mirabegron on the bladder shape, VUR and thus its crucial role in protecting the upper urinary tract.

Conclusions

Mirabegron is an effective treatment for children with therapy-refractory NLUTD with an average efficacy of 2 years after which additional therapy is required. The use of mirabegron may, therefore, delay invasive augmentation ileocystoplasty in young NLUTD patients. Our results confirm the beneficial effect of mirabegron on clinical and video-urodynamic parameters, in particular when mirabegron is used as add-on therapy in those with low-compliance bladders. Future prospective randomized studies with longer follow-up are needed in order to

confirm the long-term efficacy and safety of mirabegron in children with NLUTD.

Conflicts of interest

All authors declare to have no potential or actual conflict of interest.

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