Annals of Urological Research

Research Article
Published: 06 Apr, 2017

Clinical Outcomes of Second-Line Treatments Cycling in Refractory Wet OAB Patients before Switching to Intradetrusor Injections of Onabotulinumtoxin/A: A Real World Observational Study

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Abstract

Introduction: Persistence and adherence rates assessed for various drugs for Overactive Bladder (OAB) in real-world settings are dramatically poor, with almost 70% to 90% of patients discontinuing treatment within 1 year. We investigated the clinical outcomes of second-line treatments in a group of patients with wet-OAB, who then switched to Onabotulinumtoxin A (Onabot/A) intradetrusorial injections. Patients' discontinuation to treatment and the reasons why patients stopped their oral medications were also investigated. Comparisons with the clinical outcomes and satisfaction to treatment obtained with Onabot/A intradetrusor injections in the same patients were also assessed.

Patients and Methods: The outpatient visits charts of 125 wet OAB patients treated with second-line oral agents, who then switched to Onabotulinum toxin A intradetrusor injections, were retrospectively reviewed. We assessed the number and types (immediate or long-acting formulations) of anticholinergics (ACHs) cycled, the use of Mirabegron oral therapy, and persistence to these pharmacological agents since the beginning of treatment until patients switched to Onabot/A intradetrusor injections. Patients were classified as having tried 1, 2, or ≥3 anticholinergics, alone or in combination with Mirabegron, or Mirabegron oral treatment alone. Daily frequency of Urinary Incontinence (UI), as recorded by the 3-day voiding diary and satisfaction to treatment, as scored by a Visual Analog Scale (VAS), both obtained at the last evaluation before being included in the neurotoxin treatment regimen, were retrospectively analyzed. Any eventual side effect due to ACHs and/or Mirabegron treatment was also noted. Daily frequency of urinary incontinence episodes and satisfaction to treatment, as well as rates of discontinuation and side effects, has been investigated in the same patients following Onabot/A intravesical treatment.

Results: From January 2000 to October 2015, 125 patients affected by refractory wet OAB have been treated with ACHs and Mirabegron. Twenty-six (31%) patients assumed 2 ACHs and then Mirabegron, 21 (25%) patients cycled 3 ACHs and then Mirabegron, 13 (15%) patients cycled 4 ACHs and then Mirabegron, 15 (18%) cycled 5 ACHs and 9 (11%) patients cycled 6 ACHs. Types of ACHs used were propiverine, trospium, solifenacine, fesoterodine, oxybutynin IR and ER. Forty-one patients, more recently evaluated for their wet-OAB, have been treated only with 1 ACH before switching to Onabot/A intradetrusor injections. Overall duration of treatment increased according to the number of ACHs cycled. The median/IRQ frequency of UI episodes/day and the median (IRQ) VAS score were similarly poor across all the subgroups of patients, regardless of the number of ACHs cycled. Poor efficacy of treatment was reported by 52 (41.6%) of patients, intolerable side effects by 38 (30.4%) patients, and poor efficacy with unpleasant adverse effects in 35 (28%). After discontinuing second-line treatments the 125 patients switched to a third-line therapy represented by Onabot/A intradetrusor injections, 100 U diluted in 10 ml normal saline. Fifty-four patients received from 1 to 4 repeat injections, 36 from 5 to 9 repeat treatments and 16 patients received ≥ 10 repeat injections. For eACH sub-group of patients with different No. of injections, the median/IQR frequency of daily UI episodes as well as satisfaction to treatment, appeared to be significantly improved as compared to those obtained with ACHs and Mirabegron, as evaluated at the last follow up visit. Improvements remained constant regardless of the number of repeat injections and of the

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Received Date: *01 Mar 2017*
Accepted Date: *04 Apr 2017*
Published Date: *06 Apr 2017*

Citation:
Giannantoni A, Gubbiotti M, de Vermandois JAR, Bini V, Cagini R, Stasi SMD. Clinical Outcomes of Second-Line Treatments Cycling in Refractory Wet OAB Patients before Switching to Intradetrusor Injections of Onabotulinumtoxin/A: A Real World Observational Study. Ann Urol Res. 2017; 1(1): 1001.

length of follow up, in the majority of cases.

Conclusion: The majority of patients affected by wet OAB cycled at least 2 antimuscarinics before switching to a third line-therapy, with a consistent group cycling 5 and 6 different anticholinergic drugs. After switching to Onabot/A intradetrusor injections, the same patients found a prompt improvement in daily UI episodes and satisfaction to treatment. Thus, there is the urgent need to identify pharmacological agents with a better efficacy and safety profile in order to improve adherence and persistence to OAB second-line therapies.

Keywords: Overactive bladder; Anticholinergics; Treatment adherence; Onabotulinumtoxin A

Introduction

Overactive Bladder (OAB) is a symptomatic condition defined as urgency, with or without Urinary Incontinence (UI), usually with frequency and nocturia [1]. The prevalence of OAB in the adult population in Europe and USA ranges between 10 and 20%t and it is a cause of significant economic and Health-Related Quality Of Life (HRQoL) burden [2-6]. Like other chronic conditions, OAB typically requires long-term persistence and adherence to therapy [7]. According to the European and American clinical guidelines, current treatments for OAB are represented by behavioural modifications, oral pharmacological agents, onabotulinum toxin A (Onabot/A) intradetrusorial injections, sacral neuromodulation and surgery [8,9]. Oral antimuscarinics, and more recently the β3-adrenoceptor agonist Mirabegron, represent second-line treatments for patients affected by the condition [10]. Although antimuscarinics have been shown to improve patient's OAB symptoms, they can induce intolerable side effects as dry mouth, constipation, blurred vision, incomplete bladder emptying, and also central nervous system effects such as somnolence and confusion [11]. These adverse effects, together with low efficacy and possible economic problems for the patient, may drastically reduce persistence and adherence to treatment [12]. Indeed, it has been observed that persistence and adherence rates assessed for various OAB drugs in real-world settings are dramatically poor, with almost 70% to 90% of patients discontinuing treatment within 1 year [13]. The American Urological Association Guidelines on OAB recommend that after failure of behavioral and pharmacological treatments, Onabot/A intradetrusor injections or a form of neuromodulation should be offered to the refractory patient [14]. Indeed, it is still not clear who is the "refractory patient" and how many anticholinergics should be used in OAB patients, before switching to third-line therapies [15]. In this situation, the risk is that refractory patients are dragged along by different pharmacological therapies of undefined length, without reACHing a prompt and effective solution.

The aims of the present study were to investigate the clinical outcomes of second-line treatments in a group of patients with wet-OAB, who then switched to Onabot/A intradetrusor injections. We also aimed to assess patient's treatment discontinuation and to identify the reasons why patients stopped their oral medications. Comparisons with the clinical outcomes obtained with Onabot/A intradetrusor injections in the same patients were also investigated.

Patients and Methods

The outpatient visits charts of 125 wet OAB patients treated with second-line oral agents, who then switched to Onabotulinum toxin intradetrusor injections, were retrospectively reviewed. Participants were eligible for inclusion if they had an initial diagnosis of wet OAB in the absence of neurological diseases (i.e. Parkinson's disease, Multiple Sclerosis, spinal cord injury), prostate enlargement, bladder cancer, severe urogenital prolapse or other potential confounding lower urinary tract conditions. Presence of comorbidities such as hypertension, diabetes mellitus, obesity, depression, skeletal muscle diseases, broncopulmonary and coronary heart diseases and related pharmacotherapies have also been identified in all patients. We assessed the number and types (immediate or long-acting formulations) of anticholinergics cycled the use of Mirabegron oral therapy. Persistence to these pharmacological treatments, until patients switched to Onabot/A intradetrusor injections was observed. Patients were classified as cycling 1, 2, or ≥3 anticholinergics, alone or in combination with Mirabegron, or Mirabegron oral treatment alone. Daily frequency of urinary incontinence, as recorded by the 3-day voiding diary and satisfaction to treatment, as scored by a Visual Analog Scale (VAS), both obtained at the last evaluation before switching to the neurotoxin treatment, were retrospectively analyzed. Any eventual side effect due to ACHs and/or Mirabegron, was also recorded. The relationships between patient's age, comorbidities and concomitant pharmacological therapies assumed by the patients, persistence and adherence to treatment with second-line oral agents for OAB have been investigated. Finally, the same clinical outcomes, as daily frequency of urinary incontinence episodes and satisfaction to treatment, as well as rates of discontinuation and side effects, have been investigated in those patients who switched to Onabot/A intradetrusor injections. The results obtained after the last follow up were compared with those obtained with previous second-line therapies.

Statistical Analysis

Kruskal Wallis test with Dwass-Steel-Chritchlow-Fligner post-hoc test has been used to make comparisons on daily urinary incontinence episodes and VAS scores frequencies among the different number of anticholinergics cycled and among different onabotulinum-toxin A treatments' groups. Wilcoxon test has been applied to make comparisons between frequency of daily urinary incontinence episodes and VAS scores at baseline and after second-line and third-line treatments. All data analysis have been performed by using Stats Direct software (version 2.7.2, 2008).

Results

Second-line OAB treatments. Clinical outcomes, side effects and persistence to treatment

From January 2000 to October 2015, 125 patients affected by refractory wet OAB have been treated with second-line pharmacological agents, i.e. ACHs and Mirabegron. The mean age ± SD was 65.3 ± 24.7yrs; 114 patients were females and 11 were males. Comorbidities, as identified at the beginning of OAB treatment and at the last follow up before Onabot/A intradetrusor injections, were detected in 101 cases. Comorbidities presented variably associated, as showed in Table 1. Among the 125 patients, 84 have been treated with at least 2 different anticholinergics, and 60 of them have also

Table 1: Comorbidities identified in 101 wet OAB patients treated with a second line (anticholinergics and Mirabegron) and a third line (Onabotulinumtoxin A intradetrusor injections) treatments.

Comorbidity	No. of patients	Pharmacological agents
Bronchial Asthma	4	Corticosteroids/antihystamines.
DiabetesMellitus + Hypertension	15	Antidiabetics/Antihypertensive dugs.
Depression/anxiety	23	Antidepressants- antipsychotics.
Fibromyalgia	1	
Gastrointestinal diseases	9	Gastrointestinal antispamodics.
Hypertension alone	11	Antihypertensive drugs.
Heart diseases	3	Antiarrythmics; ACE inhibitors; β-blockers.
Obesity	13	-
Osteoporosis	16	Biphosphonates, Vitamin D and derivates.
Pulmonar enfisema/bronchialasthma	6	Corticosteroids; Bronchodilators; antihistamines.

Table 2: Frequencies of daily urinary incontinence episodes and VAS score (satisfaction to treatment) in 126 patients cycling up to 6 anticholinergics.

Frequency of urinary incontinence/day	No. of patients	Baseline Median/IQR	After treatment Median/IQR
1 ACH cycled	41	4 (4-5)	4 (3-4)
2 ACH cycled	26	5 (4-5)	4 (3-5)
3 ACH cycled	21	5 (4-6)	4 (3.5-4.5)
4 ACH cycled	15	5 (4-5)	4 (3-5)
5 ACH cycled	13	5 (3.5-5.5)	4 (3 -5)
6 ACH cycled	9	4 (4-5)	4 (3-4)
VAS score	**No. of patients**	**Baseline** Median/IQR	**After treatment** Median/IQR
1 ACH cycled	41	-	6 (5-6)
2 ACH cycled	26	5 (4-5)	5 (4-6)*
3 ACH cycled	21	5 (5-6)	6 (6-7.5)**
4 ACH cycled	15	5 (5-6)	5 (5-7)
5 ACH cycled	13	5 (4.5-6)	5 (4-6)
6 ACH cycled	9	4 (4.5-5)	5 (4.5-5.5)

*Between median VAS score in patients cycling 2 ACHs and median VAS score in patients cycling 3 ACHs (post-treatment): p=0.0032.
**Between median VAS score in patients cycling 3 ACH and median VAS score in patients cycling 6 ACHs (post-treatment): p=0.02.
Differences (after treatment minus baseline) of urinary incontinence episodes/day and VAS score, were not significant between groups of cycling patients.

assumed Mirabegronoral tablets, 50 mg/once daily following ACHs. Particularly, 2 ACHs followed by Mirabegron were assumed by 26 (31%) patients, 3 ACHs and then Mirabegron by 21 (25%), 4 ACHs and then Mirabegron by 15(15%), 5 ACHs by 13 (18%) and 6 ACHs by 9 (11%) (Figure 1). Types of ACHs in these patients were predominantly represented by long-lasting formulations: tolterodine ER, propiverine, trospium, solifenacine, fesoterodine, oxybutynin IR and ER. Forty-one patients, more recently evaluated for their wet-OAB, have been treated with only 1ACH before switching to Onabot/A intradetrusor injections, and without assuming Mirabegron (Figure 2). Mean duration of treatment for eACH single group of patients increased according to the number of ACHs used, as follows: 3.2 ± 0.9 mos in patients treated with only 1 ACH; 6.5 ± 4.8 mos in patients cycling 2 ACHs, 7.6 ± 3.5 mos in patients cycling 3 ACHs, 12.3 ± 5.1 mos in patients cycling 4 ACHs, 15.9 ± 8.2 mos in those cycling 5 ACHs and finally, 17.7 ± 8.3 mos in patients cycling 6 ACHs. With regards to baseline urinary symptoms, the median/IQR frequency of UI episodes/day was similar across all the subgroups of patients (Table 2). After different ACH treatments, no significant difference in the median/IQR daily frequency of urinary incontinence was detected as compared to baseline (Table 2). We only found a significant difference between the median/IQR VAS score in patients cycling 2 ACHs and median/IQR VAS score in patients cycling 3 ACHs, as detected in the post-treatment (p=0.0032). With regards to the post-treatment satisfaction, the median/IQR VAS score in patients cycling 3 ACH was higher than those in patients cycling 2 and 6 different anticholinergics (p=0.0032 and p=0.02, respectively) (Table 2). Adding or switching to Mirabegron 50 mg once/daily did not change neither the daily frequency of UI episodes, nor the satisfaction to treatment, which remained substantially poor in all the subgroups of patients. When considering the reasons of treatment's discontinuation, an insufficient treatment's efficacy was reported by 52 (41.6%) patients, intolerable side effects by 38 (30.4%), and poor efficacy with unpleasant adverse effects by 35 (28%) (Figure 3). The most frequently reported adverse effects were dry mouth and constipation; 8 female patients who have been assuming 4 and 5 different ACHs, complained of episodes of confusion, sleepiness and memory disturbances. We found a significant relationship between low duration of treatment and age higher than 65 years ($p < 0.05$), presence of comorbidities ($p < 0.01$) and use of polipharmacotherapies ($p < 0.01$). Forty-seven patients older than 65 years with comorbidities discontinued their treatment for OAB soon after assuming the third ACH agent, with mean ± SD duration of treatment of 5.5 ± 1.1 months. Patients younger than 65 years and without comorbidities

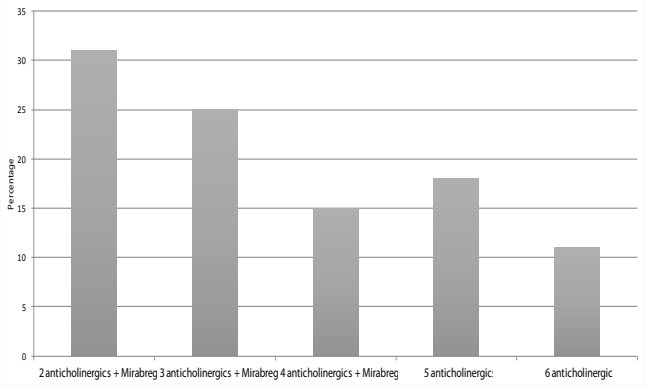

Figure 1: Anticholinergics and Mirabegron cycling in 84 wet OAB patients before switching to a third-line treatment (Onabotulinumtoxin /A intradetrusor injections).

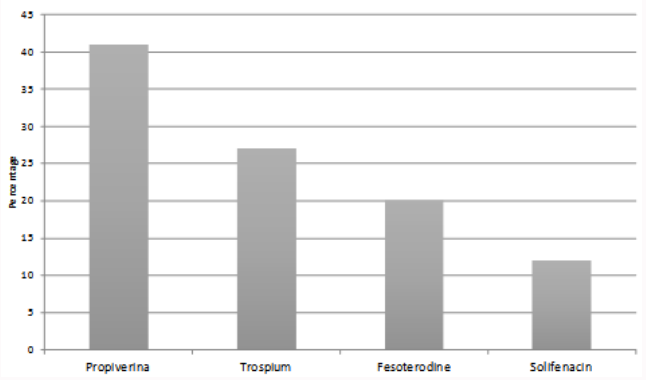

Figure 2: Types of Anticholinergics assumed by 41 patients before switching to a third-line treatment (Onabotulinumtoxin /A intradetrusor injections).

and concomitant pharmacotherapies showed a better persistence to the overall treatment, although cycling 4 or more ACHs. In these patients, the mean ± SD duration of treatment for eACH single ACH assumed was 3.2 ± 0.3 months. Frequency of adverse effects was also higher in the 101 patients assuming other concomitant pharmacological agents than in those without comorbidities: 53.4% versus 38% (p <0.01).

Onabot/A intradetrusorial injections: clinical outcomes, side effects and persistence to treatment

After discontinuing second-line treatments, the 125 patients switched to a third-line therapy represented by Onabot/A intradetrusor injections, 100 U diluted in 10 ml normal saline. Treatment details have been previously described [16]. In the majority of cases injections have been performed in an outpatient basis, under local anesthesia in the endoscopic room. Fifty-four patients received from 1 to 4 repeat injections, 36 patients from 5 to 9 repeat treatments and 16 patient's ≥10 repeat injections. Table 3 shows the median frequency of daily UI episodes as well as the median score of VAS as evaluated at baseline and after treatment for eACH sub-groups of patients with different No. of injections. The median frequency of daily urinary incontinence episodes and VAS were similar among the 3 different groups at baseline. After treatment, median/IQR of daily urinary incontinence episodes was higher in patients who received 1-4 repeat injections as compared to patients who have been treated with ≥10 repeat injections (p=0.0122), whereas median/IQR VAS scores was higher in patients who received 1-4 repeat injections

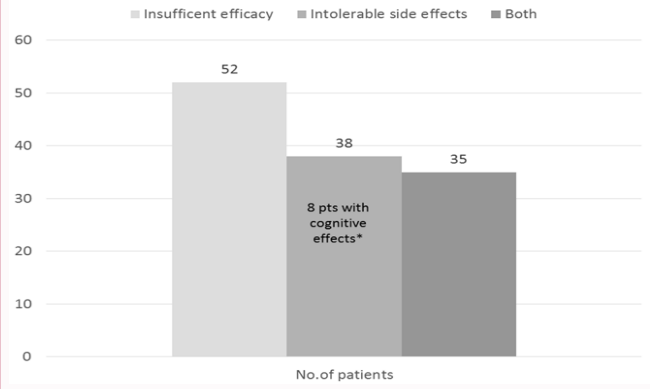

Figure 3: Second-line treatments (Anticholinergics and Mirabegron) discontinuation reasons in 125 wet OAB patients before switching to a third-line treatment (Onabotulinumtoxin /A intradetrusor injections).

as compared to patients who have been treated with 5-9 and ≥10 repeat injections (p=0.0002 and p=0.0024, respectively) (Table 3). Nineteen of these patients have been lost during follow up due to: lack of efficacy in 8 cases (after 3 and 4 repeat injections); request of a permanent solution (neuromodulation) in 4, repeat pregnancies in 2 patients, need for surgery in 3 patients (Wertheim surgical intervention in one patient, surgery for breast cancer in 2), transfer to another town in 2 cases. With regards to side effects, as recorded at the last follow up, need to perform Intermittent Catheterization (IC) due to high post-void residual volume was observed in 3 patients (for 3 months in 2 cases and 4 months in 1). Rates of bacteriuria and urinary tract infections were 18.9%, and 7.7%, respectively. Overall, we found significant differences between the median frequency/IQR of urinary incontinence episodes/day and the median/IQR VAS score, as detected after the last treatment, between ACHs and Onabot/A therapies (Table 4).

Discussion

The results of this real world observational study show that the majority of patients affected by wet OAB cycled at least 2ACHs before switching to a third line-therapy, with a consistent group of them cycling 5 and 6 different ACHs, with also Mirabegron being included in the treatment schedule. Most importantly in the present study, after switching to Onabot/A intradetrusor injections, the same patients found a prompt benefit in terms of reduction of daily UI episodes and satisfaction to treatment. In the present study, patients who assumed 5 or 6 different ACHs waited for a long time before receiving an alternative and effective solution. Notably, the response to treatment did not change regardless of type and number of ACHs cycled and of additional Mirabegron. Older patients and those with comorbidities showed a worse persistence rate to OAB second-line treatments. This could be due to an intolerable pharmacologic load in patients assuming concomitant and different drugs provided also with anticholinergic activity and to a reduced compliance to the necessary polipharmacotherapy for their pathologic conditions. Patients cycling a higher number of ACHs have been included in a treatment regimen when the use of Onabot/A therapy for OAB was still off-label. Indeed, to date the proposal of an alternative solution in our centre for patients with an inadequate response or poor satisfaction to second-line treatments occurs more quickly and 41 patients in our study cycled to Onabot/A intradetrusorial injections after only 1 ACH. Indeed, just after 1-4 repeat injections, and along all the length of follow up, the median frequency of daily UI episodes appeared

Table 3: Frequencies of daily urinary incontinence episodes and VAS score (satisfaction to treatment) in 106 patients previously cycling different Anticholinergics, who changed to onabotulinumtoxin/A intradetrusor repeat injections.

Frequency of urinary incontinence/day	**No. of patients**	**Baseline** Median/IQR	**After treatment** Median/IQR
After 1-4 onabot/A injections	54	5 (4-5.25)	1 (0-2)*
After 5-9 onabot/A injections	36	4.5 (4-5)	1 (0.25-2)
After ≥ 10 onabot/A injections	16	5 (3.25-5)	2 (1.25-2)
VAS score	**No. of patients**	**Baseline** Median/IQR	**After treatment** Median/IQR
After 1-4 onabot/A injections	16	5 (4.75-5)	9 (8-10)§
After 5-9 onabot/A injections	36	5 (4.25-6)	8 (8-9)
After ≥ 10 onabot/A injections	54	5 (5-6)	8 (7.25-8.75)

*Between median frequency of urinary incontinence episodes/day after 1-4 and ≥ 10 Onabot/A injections, p=0.0122
§ Between median VAS score after 1-4 and after 5-9 and ≥ 10 Onabot/A injections, p=0.0002 and p=0.0024, respectively.
Differences (after treatment minus baseline)of urinary incontinence episodes/day between 1-4 and ≥ 10 Onabot/A injections were significant(p=0.0146).

Table 4: Overall comparisons between frequency of urinary incontinence episodes/day and VAS score (satisfaction to treatment) after Anticholinergics treatment and after Onabotulinumtoxin A intradetrusor injection in 106 patients affected by OAB.

	Post treatment (second-line therapy) Median/ IQR	**Post-treatment (third-line therapy) Median/ IQR**
Frequency of urinaryincontinence/day	4 (3-5)	1 (0.25-2)*
VAS score	5(4-7)	8 (7-9)**

*Between median frequency of urinary incontinence episodes/day after ACHs treatment and after Onabotulinumtoxin A intradetrusor injection: p=0.0001.
** Between median VAS score after ACHs treatment and after Onabotulinumtoxin A intradetrusor injection: p=0.0031.

to be reduced as compared to that obtained in all the sub-groups of patients treated with different ACHs. Significant improvements were observed also in treatment's satisfaction in all the subgroups of patients receiving different numbers of injections. Persistence' rates at the last follow ups were similarly higher. The present study is the first to our knowledge, describing in details the clinical outcomes of second and third line treatments in the same patients affected by wet OAB. The results of the present study are in line with those of a recent retrospective claim analysis in which the burden of urinary incontinence remained relatively constant regardless of the level of anticholinergic cycling, and of whether therapy was continued or discontinued [17]. In addition, it has been demonstrated that even after initiating an anticholinergic therapy, wet OAB patients remain with substantially greater clinical and economic burden than non-OAB patients [18]. Adherence to treatment among OAB patients has been investigated by Pelletier "et al." [19] in a retrospective cohort study using anonymous, patient-level data from administrative claims. The Authors observed a low adherence rate with 14% of patients ACHieving a proportion of days covered of 80% or higher [19]. In a recent systematic review on the long-term adherence to antimuscarinic therapy in everyday practice, it was found that regardless of which specific antimuscarinic drug is studied, persistence rates are usually poor [20]. In this review, considering all drugs together, median persistence rates were 12.0% to 39.4% (with an outlier of 75.5%) at 12 months, 8.0% to 15.0% at 18 months and 6.0% to 12.0% at 24 months. The Authors identified also risk factors for discontinuation, with the most important being younger age group, use of oxybutynin and use of immediate release formulations. With regards to the clinical outcomes of Onabot/A repeat injections along previous long-term follow up studies, the results are sparse and somewhat contradictory. In the study of Dowson "et al." [21] the rate of poor efficacy of Onabot/A intradetrusorial treatment in OAB patients was low (13%), but the incidence of (IC) and bacteriuria after treatment were 21-26% % and 21% respectively, and the drop-out rate at 60 months was 25%. Indeed in this study, the majority of patients have been injected with higher doses (200U) of Onabot/A, which could have been responsible for the high rate of side effects. High rates of IC were detected also in the study of Osborne and co-workers, but patients with a preoperative PVR >100 ml and a lower threshold to initiate IC contributed to this high rate of retention [22]. In other study, the main reasons for discontinuation were, again, tolerability issues (IC and UTIs), but not lack of efficacy, even if no antibiotic prophylaxis has been given before treatment [23]. The Authors stated that potentially, initial prevention of UTIs may have permitted more patients to stay with treatment. Finally, in the study of Veeratterapillary and co-workers, the original protocol of treatment was different than that recommended today. Lower doses are currently recommended and general anesthesia is used much less often during treatment than previously. Perhaps, if in all these above mentioned studies, IC was not recommended for everyone with a PVR >150 ml, if prophylactic antibiotics were used and if the currently used doses of the neurotoxin had been administered initially, it is likely that the overall discontinuation rate would be significantly lower and the success-rate much better. One limitation of the present study is related to the great variability in past second-line treatments performed by patients, and this could represent a potential confounder in the evaluation of the results. Nevertheless this variability reflects what occurs in every day clinical practice on OAB treatment.

Taken together the results in the present study suggest the following considerations. There is the need to better clarify when and how a patient affected by OAB should be considered refractory to a second-line treatment, and how many treatment's attempt should be performed before proposing a third- line solution. There is also the need to identify pharmacological agents with a better efficacy/safety profile in order to improve adherence and persistence to treatments. Furthermore, in many wet OAB patients, the lack of response to the first second-line pharmacological agent could be enough to switch to a third-line management, as botulinum a toxin or neuromodulation. In selected cases with severe wet OAB and with a great burden on QOL, the possibility to promptly offer these alternatives should be taken into account, in order to avoid a suboptimal care in patients strongly bothered by a so disabling disease.

Conclusion

Persistence to second-line treatments in patients affected with wet-OAB is poor along long-term follow up, due to poor efficacy and

unpleasant side effects. A third-line treatment solution should be promptly offered as it allows obtaining quick and successful results.

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